present concepts

in Internal Medicine

VOL IV No 10 October 1971

165

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)

Department of Medicine

AD 740 686

2a. REPORT SECURITY CLASSIFICATION

2b. GROUP

3. REPORT TITLE

NEUROLOGY SYMPOSIUM

VOL IV No 10, OCTOBER 1971, PRESENT CONCEPTS IN INTERNAL MEDICINE* (See Item #11)

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

Symposium (medical) October 1971

5. AUTHOR(S) (First name, middle initial, last name)

Buchanan, Darrell S. (Guest Editors). Contributors: Horenstein S, Poser CM, Greenhouse AH, McCarty GE, Curtin WJ, Connor WS, Bronshvag M, Newkirk TA, Miller L, Gerow LB Jr.

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
N/A	160 (pp 823-982)	135

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
N/A	N/A
b. PROJECT NO.	
c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	N/A

10. DISTRIBUTION STATEMENT

The distribution of this document is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
Twelve symposia per year form each volume. Each symposium is on a specialty in the field of internal medicine. At this hospital Neurology is in the Department of Medicine.	LETTERMAN GENERAL HOSPITAL Presidio of San Francisco, Calif 94129

13. ABSTRACT

The papers in this year's Neurology Symposium of Present Concepts do not follow any central theme but are a "potpourri" reflecting each contributor's interests. The lead article "Perceptual Disorders. Their neurological and behavioral consequences" is a 30-page article presenting the schemes for arranging perceptual disorders hierarchically and snyoptically and the methods of examination. The titles of the other articles will provide for the reader the scope of the symposium: "Hyperglycemic nonketotic coma. The Role of sodium in its pathogenesis", "Neurological manifestations of endocrine diseases", "Remote effects of cancer on the nervous system", "Spectrum of virus infections of the central nervous system", "Some autosomal chromosome abnormalities", "Cerebral blood flow", "The management of cerebral edema with oral glycerol", "Evaluation of the dizzy patients", "Post surgical psychosis", and "Neuromuscular junction and its disorders".

The Guest Editor expresses his fervent hope that the trend for the ever-increasing interaction between Neurology and the mainstream of Medicine and Surgery will continue "so long as that object of our attentions, the patient, insists upon having so complex an assortment of organ systems serving to support the function of his brain."

DD FORM 1 NOV 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

UNCLASSIFIED

Security Classification

KEY WORDS	ROLE	WT	ROLE	WT	ROLE	WT
NEUROLOGY						
NEUROLOGICAL DISEASES						
PERCEPTUAL DISORDERS						
COMA, hyperglycemic, non-ketotic						
CENTRAL NERVOUS SYSTEM, viral infections						
VIRAL INFECTIONS, CNS						
ENDOCRINE DISEASES, neurological manifestations						
CEREBROVASCULAR CIRCULATION (cerebral blood flow)						
CANCER, Nervous system effects						
PSYCHOSIS, post-surgical						
VERTIGO (dizziness)						
Non-vertiginous dizziness						
NEUROMUSCULAR JUNCTION						
EDEMA, cerebral						

PRESENT CONCEPTS IN INTERNAL MEDICINE

GUEST EDITOR FOR OCTOBER 1971

LTC Darrell S. Buchanan, MC
Chief, Neurology Service

ASSISTANT EDITOR

Lottie Applewhite, M.S.

EDITORIAL BOARD

LETTERMAN GENERAL HOSPITAL
Presidio of San Francisco, California 94129

PRESENT CONCEPTS IN INTERNAL MEDICINE
VOLUME IV *October 1971* Number 10

NEUROLOGY SYMPOSIUM

CONTENTS

FORTHCOMING SYMPOSIA

1971	Medical Writing
	Gastroenterology
1972	Gastroenterology
	Pediatrics

FOREWORD

The papers in this year's Neurology Symposium of *Present Concepts* do not follow any central theme but are a "potpourri" reflecting the interests of residents, staff, and consultants. Our special thanks to our consultants, Doctor Greenhouse, Doctor Horenstein, and Doctor Poser, for their excellent contributions. We are indeed fortunate to have visiting professors who take such a continuing interest in our training program.

On second thought, the papers do have a theme of sorts. It is readily evident that such subjects as hyperglycemic non-ketotic coma, neurologic manifestations of endocrine diseases, and non-metastatic effects of cancer on the nervous system reflect the ever-increasing interaction between Neurology and the mainstream of Medicine and Surgery. It is my fervent hope that this trend will continue so long as that object of our attentions, the patient, insists upon having so complex an assortment of organ systems serving to support the function of his brain.

LTC DARRELL S. BUCHANAN, MC
Guest Editor

Education, *n.* That which discloses to the wise and disguises from the foolish their lack of understanding.

Esoteric, *adj.* Very particularly abstruse and consummately occult. The ancient philosphies were of two kinds, —*exoteric*, those that the philosophers themselves could partly understand, and *esoteric*, those that nobody could understand. It is the latter that have most profoundly affected modern thought and found greatest acceptance in our time.

Exception, *n.* A thing which takes the liberty to differ from the other thing of its class, as an honest man, a truthful woman, etc. "The exception proves the rule" is an expression constantly upon the lips of the ignorant, who parrot it from another with never a thought of its absurdity. In the Latin, "*Exceptio probat regulam*" means that the exception *tests* the rule, puts it to the proof, not *confirms* it. The malefactor who drew the meaning from this excellent dictum and substituted a contrary one of his own exerted an evil power which appears to be immortal.

AMBROSE BIERCE, *circa 1880*
The Devil's Dictionary
(New York Dover, 1958)

PERCEPTUAL DISORDERS: THEIR NEUROLOGICAL AND BEHAVIORAL CONSEQUENCES

Simon Horenstein, M.D.*

This discussion will focus on the disorders of perception and related clinical phenomena with major emphasis on those resulting from lesions affecting the posterior third of the cerebral hemisphere at and above the plane of the Sylvian fissure. This region of the brain includes the primary visual receiving cortex, the somesthetic sensory cortex including that part of the parietal lobe which overlies the Island of Reil and which appears specialized in relation to pain, and large areas of association cortex some of which have relatively few thalamic connections (Brodmann's area 39 and 40, the angular and supramarginal gyruses). The latter, among other things, appears to be places to which multiple sense modalities project, most importantly from visual and somesthetic areas. The underlying cerebral white matter includes extensive interhemispheric projections, especially those which regulate eye movement, fixation of gaze and the transmittal of impulses from the posterior and superior temporal lobes to parietal and frontal regions. In addition, the sector contains parts of the lenticular and caudate nuclei and all the thalamic projections to the somesthetic, auditory, and visual regions. Through its deepest portion courses the posterior limb of the internal capsule including its motor projections.

Clinical syndromes resulting from lesions in this region are frequently complex, and disorders in which impaired sensation and imperception in variable mixtures accompany one another are common. In addition, more than one modality of sensation and perception will usually be found effected simultaneously although not necessarily to the same degree. Specific function

*Professor and Chief, Section of Neurology, Saint Louis University School of Medicine, St. Louis Missouri

is invariably impaired bilaterally, even though there may be marked asymmetry from side to side. Finally, each of these clinical disorders will be found accompanied by a gross disorder of behavior. This discussion will separate the components, although I acknowledge that this has an artificiality and has only heuristic value. Additionally, emphasis will be placed on the relationship between the neurological and behavioral consequences of lesions in the posterior hemisphere, and some attention will be paid the differences between lesions involving the left and right cerebral hemispheres.

LOSS OF SENSATION

Although pure and uncomplicated loss of somesthetic or visual function resulting from lesions of the cerebral cortex or its afferent projections are relatively uncommon, that which is most likely to occur affects the visual system and results in a right or left congruous quadrantic or homonymous hemianopia. The medial margins of the visual fields are the same in each eye. The defect may be incomplete involving only a visual sector and even when a half-field is involved the defect may be more prominent in either upper or lower visual quadrant. There often is preservation of vision in the peri-macular region, so-called macular sparing. At the behavioral level the patient is aware of his visual disorder and normally compensates for it by reaching or groping to one side of space or by directing his gaze toward the affected portion of the visual field. Gaze, eye movements, and visual fixation are normal. There are usually no impairments of the ability to read, write, copy figures, name objects, or recognize faces, and orientation in space is normal.

Rarely encountered may be a hemianopic disorder secondary to a white matter lesion in

the language dominant hemisphere (usually the left) which is so located as to interrupt transcallosal projections from the right cerebrum. This results in a bimodal visual disorder characterized by contralateral (right) homonymous hemianopia and inability to read in the residual or left visual field owing to the fact that transcallosal projections from the right occipital lobe to the left parieto-occipital cortex are transected. The importance of this syndrome is its place in understanding cerebral organization.

Another infrequent disorder is one in which the lesion is in the white matter of the occipital lobe at or below the plane of the calcarine cortex. At that time a superior quadrantanopia is associated with inability to recognize faces.

A similar process may involve the somesthetic sensory cortex or its afferent projections. When the portions lying on the convexity of the hemisphere (areas 1,2,3) are affected tactile sensibility and position sense are found to be markedly impaired, and in contrast to the effect of spinal cord lesions vibration sense is often spared. The patient is as aware of his sensory loss as is the patient with uncomplicated hemianopia and attempts to compensate for it by attending to, rubbing, or otherwise protecting the affected body part. The patient is able to use the limb and digits opposite the lesion but ordinarily he does so clumsily, especially in the absence of vision, because he cannot control or regulate the use of the arm by proprioceptive and contactual means. The disorder may involve the entire side but the lips, tongue, fingers, and hand are usually most severely involved as might be expected in any lesion of the telencephalon. Incomplete loss of somesthetic sensation or vision may be accompanied by a variety of positive symptoms superimposed upon the loss itself. These include prickling and tingling in the affected extremities or flashing lights in the visual field.

Cortical deafness is not ordinarily produced by a unilateral cerebral lesion. It may occur following bilateral lesions of the transverse temporal convolution. This condition and other bilateral disorders are discussed below.

IMPERCEPTION: Amorphosynthesis and Perceptual Rivalry

Perception is a term used to describe that psychological phenomenon in which the nature and properties of a stimulus are recognized. It implies that multiple components of a stimulus are contrasted with one another, their relationships discerned, and the whole contrasted with a reference point especially the person himself, thus endowing the stimulus at a mental level with properties not inherent in it and relating it temporally and spatially to other events. Implicit in the term perception are awareness and recognition. Examples might be the distinction between roughness and smoothness or wetness and dryness. The morphological basis for perception within the somesthetic system is not yet well understood, but recent work in Hubel's laboratory on the visual system indicates that progressive averaging of the output of numerous visually activated cells on individual cells in successive order results in structures which respond to depth, rate, brightness, direction of movement, and pattern. Some current anatomical studies indicate corresponding degrees of differentiation of cells to which afferents project from vibrissae in mystacial animals.

Imperception or impaired perception as a clinical phenomenon appears to depend upon inability of the patient to summate a multiplicity of sensory events thus transforming multiple points of sensation in various modalities into a conscious mental image. This neurological defect has been called amorphosynthesis and may be divided into a hierarchy describing the severity of deficit. TABLE I.

There are certain aphorisms which may be applied to patients suffering perceptual disorder.

The process usually involves more than one modality, the most common being visual and somesthetic.

Amorphosynthesis is invariably associated with neglect or denial. The latter may be complete or explicit or incomplete or implicit, varying with the severity of the perceptual disorder.

Imperception is associated with behavioral changes which reflect the severity of the neglect or denial and only indirectly the degree of neurological defect.

Increasing degrees of awareness usually correspond either to lesser degrees of a global defect or to recovery of perceptual function within a single modality.

TABLE I

HIERARCHY DESCRIBING SEVERITY OF AMORPHOSYNTHESIS

VISUAL	TACTILE	AUDITORY
LEAST		
		Reversal of direction of auditory extinction
Inattention to one side of face	*Inattention* to one side of body	*Auditory extinction*
Inability to divide space accurately	*Inability to locate* points on body surface	*Mislocalization of the source of sound* by touch
Distortion of the coordinates of space	*Distortion* of tactile form perception	
Constructional apraxia	*Dressing apraxia*	*Apraxia for localization in auditory space by sight*
Denial of blindness	*Denial* of limb	*Agnosia* for auditory space
MOST		

VISUAL IMPERCEPTION

Disorders of visual perception as outlined in TABLE I may seem to worsen with the evolution of a progressive lesion, but is most frequently encountered in adult cases following cerebral infarction.

At the maximum level of defect the patient denies that anything is wrong with vision and insists that his field of vision is normal and complete. Visual fixation is defective and the patient lies with his head and eyes deviated toward the side of the lesion, denies explicitly that he is ill, and manifests all of the lesser degrees of visual imperception. At the maximal or agnosic level of visual imperception the patient fixes his gaze only transiently and may be unable to look at anything. He cannot discover by sight the source of voices and sounds from the side of space opposite the cerebral lesion and may conclude that people are calling to him from the next room or porch.

As the degree of perceptual disorder lessens the denial with which the patient treats the world around him becomes somewhat modified and awareness, though incomplete, becomes evident. Denial is no longer explicit but rather the patient's assessment of his defect is incomplete or incorrect and the denial is referred to as implicit. Thus, the patient may say that he needs new glasses. He copies geometric figures inaccurately, omitting that side of the figure which is opposite the cerebral lesion. This disorder of construction, inappropriately called constructional apraxia, is represented not only be incapacity to copy figures but also by preoccupation with the side of visual space ipsilateral to the cerebral lesion and virtually total neglect of the side of space contralateral to the cerebral lesion. Thus, when eating from a food tray or a plate, the patient finds and consumes only the food on

the same side as the cerebral lesion, often complaining that he has been given no butter or roll, that there was no meat on his plate, or that he is still hungry. If the tray or plate is now turned 180 degrees the patient appears surprised and resumes eating. His explanation for this event indicates his unawareness as he offers a fatuity in explanation such as the belief that someone had hidden his food. The visual perceptual field becomes broadened or constricted by the point in space upon which focusing occurs, but the patient makes perceptual errors in both visual fields although those in the field on the same side as the lesion are minor in degree, and he fails to recognize the absence of visual information arising from the visual field opposite the lesion.

The patient whose disorder permits greater orientation to visual space may display impairment of perception of the physical dimensions of space. The patient cannot estimate by sight verticality or depth. Such imperception of the coordinates of space may be seen as the patient's handwriting slants upward from the horizontal at an angle of 30-45 degrees as he writes. Similar disturbance of his angular perception is shown by a head tilt which eventually carries his occiput away from the side of the cerebral lesion and his chin toward it. His whole body may tilt in like fashion as the patient believes that only in this way can the external world appear upright.

A lesser disorder of visual perception is characterized by neglect of one side of horizontal space. The patient bisects horizontally continuous stimuli which extend fifteen degrees or more beyond the fixation point on either side toward the side of the cerebral lesion. He is most likely to display this same perceptual error in his reading and writing. Simple words such as "woman" may be read as "man," the first two letters being that part of the visual field

which is neglected. Frequently the word cannot be divided so that the portion read is a real word. The perceived word fragment may then become converted into some other word. This process is called completion, and pervades many aspects of perceptual disorder independent of the affected mode. An example of completion upon reading was provided by a patient who read the name "Harvard" as "ward" completing the "v" in "vard," the second syllable of the word "Harvard," into a real word, "ward." Completion of incomplete letters, geometric figures, faces, etc. results from the patient's unawareness of the incomplete nature of the figure just as he is neglectful of one side of other figures with which he is presented.

The least severe level of perceptual disorder is visual "suppression" or "extinction" shown by inattention to simultaneous and roughly equivalent visual stimulation on opposite sides of space. This defect may vary with summation of stimulation and has some temporal continuity. If the stimulus which is exposed in the affected portion of the visual field is made larger, a point may be reached at which the patient will report seeing both of them. It may further be shown that this process has a certain duration in time.

Examination of the patient with visual imperception

Examination for visual imperception may be carried out quickly at the bedside and should include (1) an estimation of the patient's visual field, (2) his ability to bisect horizontal lines, (3) the degree of his distortion of the coordinates of space, (4) his ability to construct a horizontally oriented figure, (5) his defect in vision (which he denies), and (6) his visual fixation.

Estimation of the visual field. This can be done by the confrontation technique described in any neurological text. However, the

confrontation field examination should be extended to include bilateral or double simultaneous stimulation. The method which seems most easily used is simply to ask the patient to look at the examiner with both eyes. An equivalent finger movement is them made simultaneously in homologous portions of the right and left visual field, and the patient is asked to report or touch where he sees movement. Some maximally affected patients will be unable to fix gaze long enough to be tested in this way and each effort at fixation is then followed by deviation of the head and eyes toward the side of the lesion.

Bisection of horizontal lines.
If the patient is able to use a pencil he can be asked to divide into equal parts a line several centimeters long. If unable to use a pencil he may alternatively be asked to place his finger on the middle of a piece of string, tape measure, or other horizontally continuous object. If the same test object at the same distance is used repeatedly the defect can be roughly quantified.

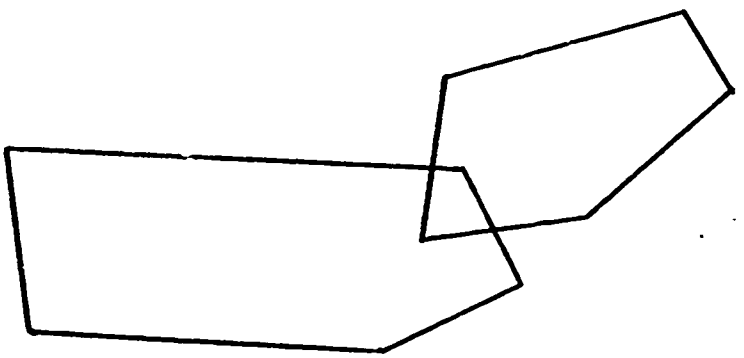
Distortion of the coordinates of space
can be demonstrated by asking the patient to write his name and address on a piece of paper and observing to what degree the writing deviates from horizontal. Alternatively, the patient can be given a stick several centimeters in length and asked to hold it parallel to the vertical edge of a door or window. Usually it will be inclined fifteen or twenty degrees from vertical with the upper end toward the side of cerebral lesion. A third method is to ask the patient to touch a small object suspended in space. A button or small ball suspended from a light thread is used. The primary movement, that is where the finger is placed before groping, is noted. Patients with disturbance of the coordinates of space usually reach below, beyond, and to one side (usually that of the cerebral lesion). When their fingers fail to find the object, groping follows and judgment

of the patient's misperception of the parameters of space depends upon observing the initial movement as most patients are able to encounter the object by groping.

Constructional apraxia is examined by asking the patient to copy any horizontally oriented figure such as an asymmetric pentagon or to arrange sticks to conform to a similar pattern. The side opposite the cerebral lesion is usually neglected. This is illustrated in Figure 1.

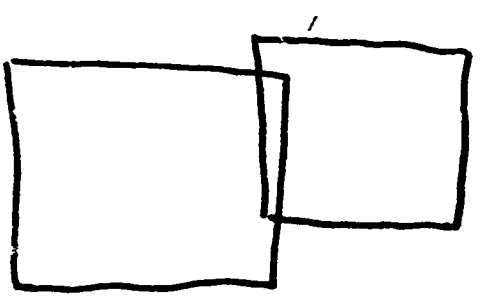
Denial of defect of vision is usually discovered by observing the patient's posture, eliciting his reason for being in hospital, and asking him directly about his vision. Where explicit denial is maximal the patient is likely to be found lying with his head and eyes firmly deviated toward the cerebral lesion asserting that nothing is wrong. He describes his environment only in terms of space on the same side as the cerebral lesion.

Defective visual fixation is conveniently examined by testing optokinetic nystagmus. This may be done by asking the patient to watch or count regularly spaced objects such as the numerals of a tape measure. The tape is drawn across the visual field from left to right and reverse. When fixation is impaired optokinetic nystagmus is abnormal regardless of the direction from which the targets enter the field, even though the abnormality may not be the same from side to side. At the most dense levels of visual imperception ocular deviation toward the cerebral lesion is enhanced virtually tonically. At lesser levels a few irregular, jerking eye movements are seen, and at the least levels uneven optokinetic nystagmus occurs. Since the function of fixation is defective, the nystagmus is irregular no matter how the objects cross the horizontal field, but the abnormality is always greater in relation to movement from the side opposite the cerebral lesion.



A. Figure patient is shown and asked to copy.

B. Patient's drawing of figure. Demonstration shows neglect of the left side of figure. This is the type most often associated with right temporoparietal lesion. This defect of constructional ability is known as *constructional apraxia.*



C. Patient's drawing of figure. Demonstration shows preservation of the spatial relationship with simplication of the figures to two rectangles. This is most often associated with left temporoparietal lesion and aphasia. The defect represents *constructional simplification.*

Figure 1.

Patients suffering perceptual disorders tire rapidly and perseverate readily. They rarely can perform more than one task at a time and often display marked agitation when they become aware that their performance is unsatisfactory. Examining periods should be kept brief, one task at a time should be requested, the patient thanked for his responses without reproof for errors, and sessions terminated upon the appearance of fatigue or restlessness.

SOMESTHETIC IMPERCEPTION

Somesthetic imperception has been ranked in TABLE I in a hierarchy similar to that of visual imperception. The maximal disorder is one in which the patient denies the existence and affection of the limb opposite the cerebral lesion. This agnostic state is characterized by explicit denial that anything is wrong with the limb or even that it belongs to the patient. If paralysis accompanies the disorder it, too, is denied. If the limb is shown the patient he may not recognize it as his own even after feeling it and may readily accept the proferred hand of another as his own, failing to recognize or account for such obvious differences as color or shape, accounting for his error by complaining, "You're the doctor - you should know" or "I'm sick - you find out." Unawareness may be so great at this time that the limb may become injured by falling between the spokes of a wheelchair without evoking an appropriate response.

Such severe degrees of perceptual deficit in any modality are unstable and fluctuant in most vascular disorders and usually improve with the passage of time or with reinforcement of attention. At lesser levels of imperception denial becomes more implicit as a degree of awareness returns. The next distinctive phase is that of dressing apraxia. The patient is

only imperfectly able to orient objects of dress including teeth, spectacles, and bedclothing to his body, performing equally badly with his eyes closed. Commonly, one spectacle bow rests haphazardly against the head on the side opposite the cerebral lesion instead of on the ear. The resulting distortion of optical axes may then be misinterpreted as meaning that the spectacles need correction. The leg or other body part on the side opposite the cerebral lesion may remain heedlessly uncovered. The patient is usually unable to dress his body owing to inability to discern the relationship between the garment's sleeves and his arms. He usually does a little better on the "normal" side. A man may not shave on the side opposite the lesion and a woman with long hair may fail to groom on that side.

Less severe disorders of perception are characterized by <u>impaired form and finger recognition</u>. The patient cannot identify objects placed in his hand owing to inability to recognize by palpation their form, texture, relative weight, wetness, dryness, warmth, or coolness. He is unable to display, recognize, or name his own fingers or limbs accurately and may become quite perplexed when asked to identify the sides and fingers of the examiner or those in a picture. The distortion of perception of body form is often easily perceived by asking the patient to find the thumb on the affected side of the body. He may reach for it at the level of the midforearm or wrist and then he gropes his way to the hand, often mistaking another finger for the thumb. At this level of disorder various derivative perceptual distortions are also present. The affected limb may feel foreshortened with the fingers perceived in cramped or distorted positions or with extra fingers growing in the midpalm. One such patient reported that he could not use his left hand because a small hand, funny and tapered like a monkey's paw, was "growing" from his wrist and if only it

could be amputated he would be well again. A recent case said that his left hand felt like ice and "inhuman".

Impaired tactile localization and two-point discrimination dominate the next less severe level of somesthetic imperception. Two-point discrimination thresholds are normally textured over the body surface so that they are highest over the back and lowest over the tip of the index fingers where two points as close as 1.0 mm or less may be detected. In perceptual disorders the two-point threshold may be infinitely high when equivalent stimuli are used, the patient reporting that which is closer to the shoulder. It often occurs that the patient's capacity to discriminate two points touched simultaneously on one side of the body is so diminished that even when such disparate points as the face and hand are touched the patient recognizes only one, usually the face. This can also be shown to be bilaterally abnormal although the abnormality on the same side as the cerebral lesion is less severe. It is usually possible to achieve simultaneous recognition by increasing the size of the neglected stimulus until finally the patient reports both of them. If one persists in increasing the size of the now recognized stimulus, a point may be reached at which there is actual reversal of the previous pattern of recognition, that is the direction of "extinction" is reversed. Extinction reversal is common to all perceptual disorders and accounts in part for moment to moment fluctuation in the details of neurological examination and is particularly evident in the auditory system. Localization of individually touched points on the body surface may also be impaired and patients unable to identify accurately the site or side which has been touched. This deficit, too, is not necessarily confined to one side of the body. When denial and neglect of one side of the body are complete, tactile localization may

be abnormal on the so-called normal side. The direction of tactile mislocalization, like that of imperception, is usually displacement toward the shoulder, hip, or center of the face.

The least level of impaired somesthetic perception is inattention to the stimulus on one side upon double simultaneous bilateral tactile stimulation of roughly homologous parts of the body. That on the same side as the cerebral lesion is ordinarily recognized while that on the opposite side is either not felt or is described as somehow different in size, shape, location, or duration. Rapid adaptation may occur on the application of a single stimulus to the affected side. Extinction, equalization, and reversal may be demonstrated in a manner similar to that described above.

As with visual disorders, progression among these levels is but imperfect and all the phenomena of the lesser levels are encountered in the denser ones. Thus, the patient agnosic for one side of his body always has impaired double simultaneous bilateral recognition, but the patient with impairment at the latter level need not be agnosic.

Examination for Somesthetic Imperception

An evaluation of somesthetic imperception should include the patient's (1) identification, or denial, of limb and side, (2) dressing ability, (3) identification of objects in his hand and numerals written on the skin, (4) localization of tactile stimuli, (5) identification of two simultaneous bilateral tactile stimuli.

Denial of limb and side are characterized by preoccupation with the limbs on the same side as the brain lesion and, independent of paralysis, neglect of the limbs and body opposite the cerebral lesion. There is explicit denial of disease on direct questioning and failure to recognize the affected limb as his own.

Dressing apraxia is discovered by asking the patient to don a jacket, gown, or robe and observing whether his inability to complete the act relates to a motor deficit or inability to discover the topographic relationship between his body and the article of clothing.

Form and finger recognition are tested by asking patients to identify objects placed in the hand or to differentiate among them with respect to size, shape, texture, and relative temperature or weight. Letters or numerals may be written on the skin. This portion of the test should be done slowly and smoothly using a polished blunt object. One's preference is to use the volar pad of the index finger holding the hand so that the orientation of the writing corresponds to letters which a patient might be reading. O,S,W, and Z are easy while E,F, and L are difficult. The numerals 3,5,6 and 2 are usually the easier. This test is difficult for the intact person and sometimes impossible for patients. It must be performed in the absence of vision and the easiest way to accomplish this is by hanging a sheet in front of the patient's face preventing his seeing his hands because asking him to do two things at once, (i.e. close his eyes and perform the test) may impair his ability to concentrate on the test.

Finger recognition and side to side orientation are tested by asking the patient to demonstrate and name sides and fingers of his own and the examiner's body on command. Some fingers, e.g. the right thumb, are readily displayed, but others, e.g. the right fourth or ring finger, are frequently missed.

Tactile localization is tested by touching the skin of the fingers and asking him to find the spot as accurately as he can. The normal person can find the smallest spot touched with accuracy and can transpose it to an outline of

the hand. Many patients either fail to understand what is asked or fail to touch accurately, tending to rub a large area. The errors in localization may be quantified and recorded. When patients are unable to comply with this test, they may then be asked to find their own thumbs or fingers and the error noted.

Two-point discrimination is tested preferentially on the volar pad or radial side of the index finger. The threshold is normally 2-3 mm. The responses again may be noted.

Care should be taken to test the "normal" limb especially when the patient is unable to dress or denies the existence of his own limb.

Recognition of simultaneous bilateral tactile stimulation is tested by touching the limbs or forehead in bilateral homologous body segments in the absence of vision. If the patient fails to report feeling one stimulus, its size may be increased until simultaneous recognition occurs and the defect thus quantified.

AUDITORY IMPERCEPTION OF SPACE

Auditory imperception of space is the least constant and least often recognized feature of the perceptual disorder which follows a gross lesion of the hemisphere. It often appears that improvement in the mental and behavioral components of the clinical disorder which follows parieto-temporal infarction coincides with improved auditory spatial perceptual function. That the latter may cause the improved behavior is suggested by the improvement in mental function which occurs as imperception lessens in other modality specific areas of loss.

Agnosia for auditory space is the densest and most severe impairment of auditory space

perception. It is characterized by disturbance of interpretation of the dimensions of extra personal space resembling that seen in the visually impaired patient. The patient believes his auditory environment to be limited to the side of space corresponding to the cerebral lesion. Even though able to hear and recognize the nature of sounds and comprehend speech coming from the side opposite the cerebral lesion, he believes them to originate from an adjacent room and cannot understand why his family insists on talking to him from another room or the porch.

Apraxia for ocular localization of the source of sound represents the next lesser level of auditory imperception. Normally one fixes his gaze quickly and within a few degrees on the source of sound in nearby space. In the type patient under discussion here, sounds originating in any part of space result only in further deviation of the head and eyes toward the same side of space as the cerebral lesion, as the patient is not only unable to locate sound sources but preoccupied with one side of space. As this condition lessens searching movements toward the source of sound are observed but are usually inadequate, ill-sustained, and unsuccessful.

Mislocalization of the source of proximate sound by touch is characteristic of lesser levels of this disorder and invariably applies only to sounds originating from the side of space opposite the cerebral lesion which are generally localized at the midline regardless of their origin. Localization of proximate sounds coming from the side of the cerebral lesion is usually accurate.

Auditory extinction is an expression of auditory space imperception and is observed when the aforementioned manifestations are present but usually is not detectable in isolation. Upon bilateral simultaneous

stimulation the patient reports only the sound adjacent to the ear on the same side as the brain lesion. Stimulus equality and reversal of extinction may be achieved by making the hitherto neglected one louder.

Extinction reversal has been mentioned previously in connection with other forms of imperception, but it is in connection with the auditory component of perceptual disorders that it is most commonly observed. Even though extinction reversal is seen with other forms of imperception it rarely is frequent and usually is not a prominent feature of the clinical disorder. In auditory space imperception it appears to be a major factor in the recovery of spatial orientation. It is detected when equivalent sounds made simultaneously outside each ear are referred to the side opposite the cerebral lesion. The reasons for the facility with which the direction of auditory extinction reverses are not known.

Examination of the Patient for Auditory Imperception of Space

An evaluation for auditory imperception should include testing for sound localization by several methods.

Agnosia for auditory space is readily discovered by talking to the patient from the side opposite the brain lesion and asking where the sound is originating. Apraxia for ocular localization of the source of sound is recognized by making a sound, e.g. jingling keys or snapping one's fingers, and asking him to look at the sound source. Localization by touch is tested by making a noise within reach and asking the patient to touch it. An easy way to do this is to scratch the pillow or rub one's fingers in the air in such a way that the patient cannot otherwise detect the source of sounds. Auditory extinction and extinction reversal are examined by making sounds

(scratching the pillow or rubbing the fingers) near each ear and eliciting the patient's responses.

SPECIAL PROBLEMS

The heteromodal character of the clinical disorder resulting from involvement of more than one modality (especially as related to vision and somesthetic function) permits interaction among the affected modalities. In general the severity of involvement in one perceptual mode parallels that observed in others. Further, mechanisms of summation and reinforcement on summation and spatial orientation result in fluctuation in the details of examination from moment to moment which further confuses the clinical picture. The patient who displays gross neglect of the limb and denial of its existence usually denies simultaneously the same side of visual space, is unable to fix his gaze on an object, and is agnosic for the side of auditory space ipsilateral the visual and somesthetic disorder. While there may be some difference in the severity of affection of the various components of the disorder, it is rarely confined to a single modality. In addition, the effect on behavior is usually distributed bilaterally. Perceptual impairment of mild degree may be seen in the "normal" limbs when maximal errors are made in the "affected" ones. The errors in construction and reading occur within the "spared" part of the visual field. Released automatisms invariably occur on both sides of the body. Such bilateral character of the disorder persists throughout the illness. Moreover, improved orientation in space follows lessening of the defect in even one area. The effect on spatial orientation of improving auditory perception of space has already been noted. However, the reverse may occur as well. Thus, any event occurring in the sensory field on

the same side as the cerebral lesion may result in the "extinction" of recognition of an event occurring simultaneously on the side of space opposite the lesion. Movement within the visual field ipsilateral to the brain lesion may, for example, result in the patient's failure to recognize that he has been touched on the side of the body opposite the lesion. Since each "extinguishing" event has a continuing influence or after effect, the process becomes continuous and events in visual and somesthetic space lend continuity to the failure of bilateral simultaneous recognition and hence prolong the neglect, denial, and corresponding behavior and mental disorder.

Perceptual rivalry is a term which has been applied to that component of perceptual disorder in which suppression or extinction takes place in relation to bilateral stimulation which is usually heteromodal. It is separate from the disturbance of perception itself although it co-exists with it. That this is so can be shown by identifying disordered perception on either side of the body, field of vision or auditory sphere when adventitious stimuli are minimal. It is only when there is interaction among stimuli that perceptual rivalry appears. Its result is continuing diversion of attention to adventitious stimuli arising on the side of the cerebral lesion at the expense of operant ones coming from space opposite the brain lesion. The usual extinction of the former by the latter being lost, the stimuli as indicated need not be of the same order. The net result is the pre-emption of attention by trivial events. It is currently the fashion to attribute this phenomenon to competition between the two hemispheres for the arousal resulting from reticular activation. At the present time evidence that this is so is lacking, although reinforcement of attention by corticoreticular systems may be defective. Data obtained by us and our

colleagues suggest that the normal interaction between stimulation of the two hemispheres which normally permits extinction and suppression of parts of one hemisphere by the other is somehow impaired, possibly by reticular or callosal mechanisms. Such phenomena as extinction reversal suggest that the problem is much more complex than simply competition for greater access to reticular activation. Rather, control mechanisms seem affected at several levels.

Bilateral imperception rarely occurs except in the context of diffuse disorders such as multiple metastases, degenerative disorders, or extensive white matter disease. The horizontal bias described above is absent, and the patient displays a severe agnosia for the loss of function, often continuing to behave as though he were able to see and offering such explanations as his glasses are dirty to account for his errors. Owing to failure of any visual stimuli to provoke a response, the denial of blindness is accompanied by unresponsiveness to visual stimulation and ocular immobility. Lesser levels are associated with inability to read, inability to orient one's self in visual space, and inability to find one's way even in familiar surroundings. The somesthetic disorder is marked by immobility of the limbs, marked errors in localization of points on the body surface, inability to recognize that the body has been touched or moved, and a sort of analeptic stupor. Many such patients have language disorders and most are unable to name or otherwise symbolize objects placed in the hand for identification or points touched on the body. The auditory counterpart is neglect of auditory space bilaterally, cortical deafness, and often a severe language disorder with agnosia for the loss.

When aphasia and related agnosic disorders occur in patients with left cerebral lesions some aspects of the visuo-spatial disorders become altered by the attendant aphasia. This is readily seen upon attempting to test lexical, constructional, and graphic disorders. Moreover, in progressive disorders such as metastatic disease, the evolving aphasia has been shown progressively to "undercut" the perceptual disorder, the features of which become decreasingly evident. At any level, however, certain features are common to parieto-temporal lesions occurring on either side of the brain. These include neglect of one side of space, denial of disease, defective orientation to parts of the body or toward one side of visual space. The defect of constructional ability observed shows major differences from the one seen in patients with nondominant (usually right) hemisphere lesions - in aphasic disorders, the figure reproduced under direct vision becomes simplified rather than showing evidence of spacial neglect, i.e. the five-sided figure is drawn as a four-sided one without neglect of one side. Figure 1C. Agnosia related to impaired language function may so alter symbolic processes that the horizontal bias of perceptual disorders may be seen to be absent. Studies of patients with progressive or recovering disorders suggest that this is attributable to the component of the disorder of hemisphere function which causes the aphasic state.

Paralysis of the face, arm, and leg may accompany disorders which lead to inattention. Pathological studies of our own case material disclose either extensive involvement of the major portion of the affected hemisphere or transection of the hemisphere to involve the posterior limb of the internal capsule. Paralysis (as opposed to neglect and resulting disuse) is not seen with parietal cortical

lesions alone, but there may be profound persistent reduction in tone of the opposite limbs, especially the upper. It can be so severe that subluxation of the shoulder occurs in the first minutes of the illness and is found on initial examination. Throughout much of the illness flaccidity dominates the postural tone of the hip, shoulder, elbow, and knee. Spasticity occurs late and is mild when it does, and is most prominent in the wrist and finger flexors. The dystonia which ensues upon this sort of lesion results in only slight flexion at the wrist and metacarpophalangeal joints and some 30-60 degrees of flexion at the interphalangeal joints. The hand readily becomes puffy and the capsule of the affected shoulder later becomes painful. Flaccidity accompanied by defective supporting reactions affects the lower limbs for long periods and the quadriceps and hamstring muscles, although strong enough to do so, fail to maintain the knee upon standing, resulting thereby in genu recurvatum, postural instability, and occasionally injury to the genicular ligaments. In severe cases dystonic flexion may occur at the hip and knee while the elbow is extended and the hand held in the manner described.

Postural abnormalities are present throughout the illness assuming several forms. At the maximal level of imperception there is tonic deviation of the head and eyes to the side of the cerebral lesion. When patients can sit unsupported, the head may be found deviated so that the occiput is inclined away from the lesion and the face turned toward it and somewhat upward. When the patient stands the entire body may be inclined in this direction. These abnormalities persist to some degree throughout the clinical course and can sometimes be shown to result from visual stimulation as the deviation of the head becomes corrected when the patient is placed in a dark room or the eyes are covered.

Automatisms of various types are often released when the cerebrum is altered by disease. That automatism which accompanies lesions of the parietal lobe and is common in perceptual disorder is called the avoiding response. As far as we know movement does not result from the positive action of parietal elements but rather originates elsewhere, having been released by such lesions. "Avoiding" has three common and easily discovered components — tactile, visual, and peri-oral. The former is elicited by stroking the palm gently, particularly on its ulnar side. Care should be taken to keep the stimulus tactile. Such stimulation is followed by extension of the wrist and fingers and abduction of the fingers. In some cases the entire arm becomes elevated and may be maintained in this position for several minutes. The hand on the same side as the cerebral lesion (the "normal" one) displays this response as well as the hand opposite the brain lesion. The avoiding response is not seen in paralyzed limbs. Visual avoiding is most easily seen when the patient is erect and the head unsupported. At that time stimuli approaching the face result in retraction of the head, extension of the neck and occasionally closing the eyes. Pursing of the lips, retraction of the tongue, and closing the jaw follow gentle tactile peri-oral contact.

"Thalamic" pain, an uncommon condition in which the patient develops severe causalgic pain in the limbs, especially the hand, following a cerebral lesion, appears also to be a perceptual disorder. This condition seems not to result from a lesion in the thalamus, but rather one which interrupts thalamic projections to that part of the somesthetic cortex which is deep to the Sylvian fissure and overlying the Island of Reil. This has been verified by a number of anatomical studies. Our own study of a single

clinical case indicated rather extensive disturbances in the perception and localization of painful stimuli on both sides of the body but much greater on the side opposite the cerebral lesion. Perception of the nature and location of minimal stimulation was seriously impaired and rapid summation occurred resulting in burning dysesthesias which were poorly localized and defined and frequently misplaced even to the other side of the body. During the maximal phase of this patient's disorder, similar changes of lesser magnitude were observed in the "normal" hand. Management is assisted by a tendency toward improvement and is symptomatic at best. Persistent cases may be refractory to all forms of drug treatment and addiction is not unusual. We have had no satisfactory experience with analgesics, hydantoins, diazepam, or chlorpromazine.

As yet there have been no callosal syndromes confirmed in which a perceptual disorder has been isolated to one part of the body as is seen in reading disorders in the left visual field. Studies of humans following callosal section in the treatment of epilepsy suggest that organization of the right parieto-temporal region is in terms of spatial relationships while the left is organized in terms of temporal relationships. Since these patients had severe seizures often following early life brain damage and in some instances severe sensory disorders were present before surgery, interpretation of these data is still incomplete.

Mental changes occur with great frequency in cases with perceptual disorder in our experience, and seem nearly universal. These include hallucinations, both visual and auditory, which sometimes are highly systematized, vivid, well-recalled, often horrifying, and which curiously are treated with a degree of neglect which appears to be in proportion to that which

is applied to all the other manifestations of the perceptual disorder. These usually are transient and occur when the patient is at an intermediate level of involvement. Frequently the patients are suspicious and referential in their thinking but this seems no different in nature although in degree from that encountered in patients with such simple sensory disorders as presbyacusis. There may be general disturbances of mentation, memory, orientation and judgment but most disorders of mental function appear to be projections of the unawareness, denial, neglect, completion and corresponding fatuous explanations to account for illness which pervade the responses to the focal disorder itself. There are occasionally disturbances in the use of language with right parieto-temporal lesions, and left-sided lesions are invariably associated with a receptive language disorder. Two distinctive abnormalities are evident in patients with right-sided lesions. The first is a change in the prosody or rhythm and inflection of speech. Emitted speech tends to be more rapid, more highly inflected at the end of a sentence, and the meter which formerly characterized the patient's speech is more staccato in character, with each syllable receiving more nearly equal emphasis. This change is apparent to nurses and the patient's family although it may not persist. A few right-handed patients with right cerebral lesions have difficulty naming objects on visual presentation when the defect is maximal but this is usually evanescent. Language, however, is often concrete and sometimes curious puns are employed. A patient asked to display his left hand may raise his right having earlier demonstrated his right hand correctly and then he accounts for his error by joking, "It's left, I'm right" or "That's right, you're wrong." At other times the patient simply shrugs off his errors and suggests that the doctor figure it out since that is what he is being paid for. Occasionally when surrounded by many people and forced to adapt to a busy environment or confronted with evidence

of his errors, a patient becomes withdrawn and silent or at other times agitated and referential, accusing the examiner of trying to "mix me up". When overwhelmed by evidence of persistent and repeated failure a patient may become totally unable to function, failing miserably or giving up altogether. This "catastrophic reaction" can be precipitated in almost any patient and the skillful examiner or physician responsible for the patient's care is careful to plan the demands to be made upon patients by professional personnel so as to avoid this form of annoying behavioral decompensation. Fatigue occurs rapidly in a patient with perceptual disorder and is correspondingly accompanied by a decline in the level of performance. Lethargy, tranquilizing and sedative drugs, dehydration, fever, a fresh cerebral lesion elsewhere, and raised intracranial pressure also decompensate performance.

Hitherto our discussion of perceptual disorders has been largely limited to the effects of cerebral infarction because that appears to be the most frequent cause of imperception associated with specific or focal lesions. Other local disorders such as tumor, abscess, trauma, subdural hematoma, and arteriovenous malformation may be associated with perceptual disorders. Generalized diseases of the brain such as senile dementia, Alzheimer's disease, and progressive multifocal leukoencephalopathy may include perceptual disorders inter alia. Degrees of imperception may also complicate toxic, metabolic and degenerative disorders. The great advantage of studying vascular cases lies in the constancy of the clinical picture and the opportunity to observe recovery from maximal levels of severity.

PROGNOSTIC FACTORS

Factors which determine the course and outcome of conditions associated with imperception or any cerebral lesion include:

The locus of the lesion. Not only is the site of the brain crucial, but also whether cortex or white matter is involved. A rather small lesion in the temporal isthmus is often capable of causing much greater functional disturbance owing to widespread cerebral disconnection than are much larger focal cortical lesions.

The rate of progression has great importance because acute lesions do not allow for the compensation which may accompany slowly evolving ones and thereby "masking" much of the clinical disorder.

The age of onset is crucial. Lesions in the parietal region in the first few years of life are uncommon. The few which have been studied appear to cause an entirely different degree of perceptual disorder than comparable ones acquired after late childhood or adolescence. They do cause hypoplasia of the opposite limbs. Such normal perceptual functions as double simultaneous visual or tactile recognition do not develop until a mental age of near 100 months. Lesions before that time thus allow compensation by the plasticity of the developing brain.

The state of the remainder of the brain appears to be an important factor as older patients with senile dementia or those with extensive bilateral brain disease as in hypertension appear to display greater deficiencies for the same size and locus of lesion than those without such widespread defects.

The nature of the process is often a determinant as vascular lesions tend to stabilize and recover while degenerative disorders continue to worsen.

The nature, effectiveness, and appropriateness of treatment, particularly in cases

of trauma and tumor, are important factors in determining the outcome of disability and the degree of widespread cerebral change. In one's own experience direct trauma as in open brain wounds tends to produce a relatively superficial lesion which leaves the patient with rather minor degrees of imperception. Glial tumors, encapsulated hemorrhages, and deep white matter infarcts wreak the greatest havoc.

CONCLUSION

Disorders of perception occurring in the human patient are usually heteromodal, are characterized by a disorder of perception of personal, juxta personal, and remote space, most often involve visual and tactile elements, and are invariably bilateral in their effect. The disorder of perception is attended by one of attention resulting from a persistently biased outcome of perceptual rivalry. Schemes of arranging perceptual disorders hierarchically and synoptically and method of examination are presented.

HYPERGLYCEMIC NON-KETOTIC COMA

The Role of Sodium in its Pathogenesis

Charles M. Poser, M.D.*

Since Sament and Schwartz /1/ called attention to hyperglycemic non-ketotic coma, several possible pathogenetic mechanisms have been proposed to explain both the lack of ketosis and the neurologic manifestations of this unusual and dangerous complication of maturity onset diabetes.

Although many authors have stressed the importance of hyperosmolality, the purpose of this paper is to call attention to the vital role of total body sodium depletion in the pathogenesis of the neurologic manifestations of this syndrome.

In a recent excellent review based on a survey of 84 patients, McCurdy /2/ pointed out that the syndrome could be traced in about half of the cases to infections, acute gastroenteritis, pancreatitis, and severe burns or to treatment by dialysis or drugs such as thiazides, steroids, diphenylhydantoin and diazoxide. The syndrome begins inconspicuously in almost all patients. Because they do not develop ketosis, their pre-coma phase is much longer than in the typical diabetic ketoacidosis, usually developing over the course of several days. At least half of the patients are comatose on admission, most are severely dehydrated and azotemic, and one-third to one-half are in metabolic acidosis from renal failure, shock or lactic acidosis. The mortality rate is over 40 percent.

*Professor, Department of Neurology, College of Medicine, University of Vermont, Burlington. Chief, Department of Neurology, Medical Center Hospital, DeGoesbriand Unit, Burlington, Vermont

According to the laboratory data reviewed by McCurdy /2/ the only reliable diagnostic observation is the striking degree of hyperglycemia without ketosis. In her series of 84, the average serum glucose was 1096 mg/100 cc with a range of 400 to 2760 mg/100 cc. The calculated serum osmolality averaged 353 mOsM/kg of water with a range of 268 to 465. In regard to the serum sodium, the average was 141 mEq/L ranging from 119 to 188 mEq/liter.

Hyperglycemic non-ketotic coma may result from different pathogenetic mechanisms. Certainly the metabolic dysfunction is complex. There may also be different clinical types of this syndrome. Assan and his associates /3/ have divided the non-ketotic metabolic comas in diabetes into the following groups — hyperosmolar, those with acidosis secondary to acute limb ischemia, those with lactic acidosis, and those with "complex electrolyte disturbances". The latter group by definition includes those patients who are severely hyponatremic.

In considering various pathogenetic mechanisms for the syndrome, particularly in regard to the neurologic manifestations, the following factors must be kept in mind. First, since the metabolic abnormality begins insidiously, becoming increasing apparent after several days, it must be assumed that a state of equilibrium has been reached between the various compartments of the body, in particular blood, brain and cerebrospinal fluid (CSF). By all measurements available /4/ the substances which are exchanged in these three compartments reach equilibrium in a matter of hours. It is therefore inappropriate to compare the changes in water, glucose, and electrolytes seen in patients with hyperglycemic non-ketotic coma with those noted either in acute animal experiments, in diabetic ketoacidosis, or in other acute human conditions. This steady state must also be kept in mind when considering osmolality

measured by the freezing point method as a diagnostic index as opposed to calculating effective osmolality in which urea should not be included. Since urea is free to move across all membranes in response to its concentration gradient, it does not exert sustained osmotic pressure. The osmotic contribution of urea will however be included in the measurement of osmolality by freezing point depression. /2/ The effective osmolality is calculated by the formula Posm = 2x serum Na (mEq/L) + blood sugar (mg/100 cc)÷18.

The extremely important osmotic effect of the serum glucose must also be remembered, as well as the limitation of glucose transport from blood to brain and to CSF. In the presence of high serum glucose levels this transport system becomes saturated, and therefore limited as was well demonstrated by Fishman. /5/ After the steady state has been achieved, this results in a significant and constant difference between serum and CSF glucose levels.

Finally, it must be stressed that hyperglycemic non-ketotic coma is the end-state of a severe metabolic dysfunction. There have been few opportunities to study the progression of the metabolic changes as the syndrome develops. There are also almost no data on the CSF glucose content, and none on the cation content of CSF in these patients. It is important, therefore, to try to evaluate the data obtained on admission as to whether they are caused by, or result from the metabolic disturbance.

In order to examine the various possible pathogenetic mechanisms and the dynamics of the metabolic disequilibrium, the components of the syndrome will be looked at separately.

Hyperosmolality

Some investigators have considered hyperosmolality the most important component of hyperglycemic non-ketotic coma. Nevertheless, Tyler /6/ pointed out that "among the recorded cases of the syndrome the correlation between absolute or estimated osmolality and the severity of the neurologic manifestations was not very good."

The effect of altered plasma osmolality upon brain fluid and electrolytes depends upon the rate with which brain water equilibrates with plasma water when a gradient in water potential develops as well as the degree to which brain solute content is altered (because the latter influences the final distribution of water). In this syndrome, however, by the time the patient is in coma, equilibrium has been reached.

The possible dangers of using the freezing point method of measuring osmolality instead of calculating the effective osmolality based upon the measured concentration of solutes have recently been emphasized. /7/ Considering 300 mOsm/kg H_2O as the upper limit of normal serum osmolality, it is interesting to examine some reported cases. For example, Maccario /8/ reported upon seven cases of the syndrome in two of which osmolality had been measured as elevated (Posm = 355 and 399). This was due at least in part to the high level of blood urea nitrogen. If the effective osmolality is now calculated on the basis of sodium and glucose concentrations, in six of her seven cases the plasma osmolality data are respectively 308 (measured at 355), 299 measured at 399, 315, 291, 301 and 300 mOsm/kg H_2O.

In two cases reported by Godeau and his co-workers /9/ the lack of correlation between the neurologic status and the osmolality is well illustrated. In the first case, the patient was comatose having a serum glucose of 1,070 mg/100 cc and serum sodium of 132 mEq/L for a calculated effective serum osmolality of 324 mOsm/kg H_2O. Seventy-two hours later, following treatment, the patient was fully awake and free of neurologic symptoms although his calculated effective serum osmolality was still 324 mOsm/kg H_2O, the serum glucose was 511 mg/100 cc and the serum sodium was 148 mEq/L. In their second case, the patient was comatose and had a calculated serum osmolality of 368 mOsm/kg H_2O, a serum sodium of 139 mEq/L and a serum glucose of 1,600 mg/100 cc. Twenty-four hours later, he went into status epilepticus and died. Immediately before death, the serum glucose was 370 mg/100 cc, and the serum sodium was unchanged at 139 mEq/L so the serum osmolality had dropped to 298 mOsm/kg H_2O.

Arnaud and his colleagues /10/, basing their consideration upon extensive clinical experience, established strict criteria for what they called hyperosmolar coma in diabetes. These criteria are (1) absence of ketoacidosis, (2) positive evidence of diabetes, either before the onset of the coma or after recovery, and (3) plasma osmolality above 340 mOsm/kg H_2O resulting from both hyperglycemia and hypernatremia. According to these authors /10/, severe dehydration acts as a trigger for the pathogenetic mechanism. Unfortunately their theoretical discussion is based upon the results of acute experiments and observations and fails to take into account transport mechanisms at the blood brain and blood CSF barriers. Even using these criteria, hyperosmolality and cerebral dysfunction are not well correlated. This can be illustrated by two of the French cases. In case three of Labram and Jacques /11/,

a 70-year-old patient, who was disoriented and who had a serum sodium of 141 mEq/L, blood glucose of 825 mg/100 cc, and serum osmolality of 328 mOsm/kg H_2O, became mentally normal and alert after rehydration. His serum sodium was 150 mEq/L, his blood glucose was 310 mg/100 cc and his Posm had risen to 345 mOsm/kg H_2O. In their case four, the patient was comatose when his Posm was 350, conscious but disoriented when the Posm was 369, but continued to deteriorate mentally with a Posm of 321 mOsm/kg H_2O.

Many of these patients are severely azotemic and although the level of urea should not be used in the calculation of osmolality, the uremia may well be a factor in causing the central nervous system dysfunction.

Hypernatremia

Other authors /3, 10/ have regarded hypernatremia as the mechanism causing the cerebral dysfunction. Almost all of them have based their hypothesis on observations in acute cases and in acute experiments in which the serum sodium rose quickly thus not permitting equilibration between the serum and the brain, while water was drawn out of the central nervous system causing acute cerebral dehydration. In so doing they failed to take into consideration the important role played by the blood brain barrier in such instances as well as the fact that these changes were acute. They also overlooked the fact that hyponatremia is present on admission as frequently as hypernatremia. In Sament and Schwartz's original case report /1/ the serum sodium on admission was only 128 mEq/L. The observations of Espinas and Poser /12/ even though they were also made in acute experiments do not support this view. They produced left hemiparesis in three groups of dogs by ligating the right middle cerebral artery at its origin from the internal carotid artery and investigated the

relationship of hyperosmolality and focal neurologic deficit. After recovering from the postoperative left hemiparesis, each of the first groups of dogs was given a rapid infusion of 200 mg of 25 percent mannitol; each of the second group was subjected to peritoneal dialysis with isotonic sodium-free solution; and each of the third group was rapidly infused with 200 ml of hypertonic salt solution containing a total of 700 mEq of sodium. All three groups were observed continuously for the development of neurologic deficit. Infusion of mannitol produced hyperosmolality, hyponatremia and left hemiparesis; peritoneal dialysis produced hyposmolality, hyponatremia and left hemiparesis; and infusion of hypertonic sodium chloride produced hyperosmolality and hypernatremia but no left hemiparesis. Thus, the dogs in the first two groups which developed hemiparesis were both hyponatremic. Both hyperosmolality and hyposmolality produced hemiparesis, but only when there was hyponatremia. For this reason, they felt that the hemiparesis resulted from hyponatremia rather than from changes in osmolality. They also believed that although the dogs had made a clinical recovery, the cerebral infarction produced by the middle cerebral artery ligation had impaired the blood brain barrier in that area. There was, therefore, a detective barrier to the exchange of either water or sodium in these animals. They concluded that neither hypernatremia nor hyperosmolality could be considered as factors in the production of cerebral dysfunction under these conditions.

Although no evidence of hyperaldosteronism has been demonstrated with hypernatremia in these patients /10/ mechanisms for its appearance are evident. Increased plasma oncotic pressure has been shown to increase sodium reabsorption and salt depletion has been demonstrated to reduce renal hemodynamics and enhance the output of renin and aldosterone. Almost all these patients are severely

dehydrated which suggests an increased plasma oncotic pressure, and many have peripheral vascular collapse with systemic hypotension and reduced renal blood flow. /13/

Hypernatremia may also be the result rather than the cause of the cerebral dysfunction. Several authors /14/ have suggested that the sustained hyperosmolality may be caused by an elevated osmotic threshold for release of antidiuretic hormone (ADH). In such a disturbance urine would be concentrated and water conserved only at an extremely high level of plasma osmolality. Thus, a new steady state at a higher plasma osmolality would be maintained by the "upward" resetting of the hypothalamic osmostat. DeRubertis and his co-workers /14/ have also presented evidence that in some patients the inadequate release of ADH was not the result of changes in osmolality but appeared to be controlled by alterations in the effective blood volume. This is perhaps the mechanism at work in patients with severe peripheral vascular collapse, assuming that the hypothamic lesion is an integral part of the cerebral dysfunction caused by the earlier metabolic changes.

It is also possible that the hypernatremia may represent the end-result of several different pathogenetic mechanisms at play in the same patient. Nevertheless, hypernatremia per se does not militate against total body salt depletion. The case reported by Johnson and his associates /15/ illustrates this possibility. In it the serum sodium went from 154 to 159 mEq/L after the patient received a total of 5,800 ml of intravenous fluids containing a total of 68.5 mEq of sodium. At the same time the hematocrit dropped from 53 to 44 percent and the patient's weight increased from 137 to 145 pounds. Coincidentally, the serum osmolality dropped from 364 to 331 mOsm/kg H_2O. Several similar instances have been reported elsewhere. /3/

Hyperglycemia

The important and probably primary roles played by hyperglycemia and glycosuria in this syndrome have been well summarized by McCurdy /2/ — when blood glucose concentration rises above the renal threshold, glucose will appear in the urine. The higher the hyperglycemia, the greater the renal excretion. Since glucose is an osmotic particle, it interferes with the renal absorption of water and therefore increased urine flow rate, at the same time it prevents maximal urine concentration even in the presence of ADH. The increased flow rate of urine through the tubular system also prevents normal sodium reabsorption, even though systemic sodium balance may demand maximum efforts to retain sodium. Prolonged osmotic diuresis eventually leads to sodium depletion (unless sodium intake is maintained) and extracellular fluid volume depletion. The osmotic diuresis itself will prevent normal renal mechanisms from retaining precious sodium or water and, unless intake can match losses, hypovolemic hypotonic dehydration is inevitable. Since there is no ketosis in this syndrome the illness follows a slow course not possible in diabetics with ketoacidosis. The longer period of time thus accounts for the more profound osmotic diuresis and dehydration observed in these patients. /15/

Many patients with this syndrome also have pyelonephritis /15/ which tends to reduce water and salt conservation. Many of these elderly patients take digitalis preparations, diuretics, and are on low sodium diets. These factors should not be overlooked as possibly contributing to salt depletion. The syndrome has been precipitated by the use of natriuretic agents such as the thiazides. /2/

Because of the limitations of the glucose transport system at the blood-brain and blood-CSF barriers, a highly significant difference in glucose levels exist. For example, in Maccario's cases /8/, the ratios of blood glucose to CSF glucose of 750/445, 1,000/680 and 426/224 result in a potential osmolal deficit (calculated on the basis of glucose (mg/100 cc) ÷ 18 = 1.0 mOsm) respectively of 17, 18 and 11 mOsm. In four cases reported by Assan and coworkers /3/ the serum/CSF glucose measurements were 450/250, 375/220, 1,500/250, and 800/500; and so the potential osmolal deficit would be respectively 11, 8, 64 and 16 $mOsm$. This potential deficit would have to be compensated for in order to maintain isomolality of blood and CSF. Although this difference has been recognized for many years, and a mechanism for it was well demonstrated by Fishman /5/, it has not been considered by writers discussing hyperglycemic non-ketotic coma.

After reviewing the available articles on the syndrome, two factors emerge as paramount in importance (1) total body depletion of sodium and (2) the existence of a significant osmotic gradient between the blood and the CSF.

SODIUM: Its Role

Davson /4/ has established that the blood, brain, and CSF are isosomolal in man. While there is a lag of several hours in establishing this isosmolality in acute changes, a steady state must be considered to exist in these patients by the time they are brought to the hospital with neurologic manifestations. Katzman /16/ has clearly demonstrated that brain osmolality is the same as that in serum although the brain contains 20 to 26 mEq/L more cation than does serum. Potassium, calcium, and magnesium contents are roughly the same and sodium accounts for this difference.

It is important, however, to differentiate between intracellular tissue and the brain extracellular compartment. Davson /4/ has demonstrated that the brain extracellular compartment can be considered as being the same as CSF as well as continuous with it. It has also been known for many years that the characteristic intracellular ion in brain is potassium whereas the characteristic extracellular ion is sodium. Katzman, Graziani and Ginsburg /17/ have confirmed the fact that in the presence of striking changes in serum and body electrolytes the potassium, calcium and magnesium concentrations of CSF remain constant. The mechanism for this is still poorly understood. This would mean that the hypokalemia which is inevitably present in the hyperglycemic non-ketotic syndrome probably plays only a minor role, if any, in the pathogenesis of the coma. Holliday, Kalayci and Harrah /18/ considered that the changes in brain cell potassium content which they observed during chronic hypernatremia and hyponatremia might be an adaptive mechanism to minimize extracellular fluid osmotic influences on brain cell volume. Bradbury and Kleeman /19/ have demonstrated that in chronic hypo-and hypernatremia, isotonicity of the whole brain with respect to plasma and CSF is partly maintained by loss or gain of sodium and chloride by the brain. The isotonicity of the intracellular fluid seemed to be maintained partly by gain or loss of water and partly by the exit or entry of potassium.

Davson /4/ has stated that gradients of diffusion from one compartment of the brain to the other usually favor diffusion to CSF and that the brain tends to equilibrate with CSF rather than with plasma. Because the composition of CSF tends to remain constant even with great changes in plasma constituents, the CSF is able to assist, by its sink action, in maintaining a similar homeostasis so far as

the brain extracellular compartment is concerned. This was confirmed by Wakim /20/ in a series of experiments with dogs. When low sodium dialysis was performed while maintaining serum osmolality with 25 percent mannitol, the mean changes in sodium were respectively -49 percent in serum, -38 percent in brain and only -8 percent in CSF.

The possibility that many if not all of the patients with the syndrome under discussion suffer from severe total body sodium depletion is supported by the fact that so many of them are in hypovolemic shock at the time of admission. Zierler /21/ believes that this state is not only a late sign of pure water loss but almost always implies associated sodium deficit. As McCurdy /2/ has noted the serum sodium concentration offers limited help in estimating the state of sodium balance.

HYPOTHETICAL MECHANISM FOR PATHOGENESIS OF NEUROLOGIC SYMPTOMS

To establish a hypothesis explaining the development of the neurologic manifestations of hyperglycemic non-ketotic coma the following are considered essential features: (1) the slow, progressive onset of symptoms without ketosis; (2) the high levels of serum glucose leading to osmotic diuresis and total body salt depletion without salt replacement; (3) equilibrium in exchanges of glucose, urea and water in blood, brain and CSF; and (4) the gradient in glucose concentration between blood and CSF, and as a result, the existence of a theoretical osmotic gradient between serum and CSF on the basis of respective glucose levels, with isosmolality of serum and CSF.

Since this theoretical osmotic gradient cannot exist, in view of the well documented isosmolality of serum, brain, and CSF, it must be made up by another solute. In the light of

Wakim's experiments /20/, it is logical to suggest that this osmotic deficit is made up by sodium ions. No data exist regarding the concentration of sodium in the CSF of patients with hyperglycemic non-ketotic coma. The following mechanism is postulated: in order to achieve isotonicity of blood, brain, and CSF, when the body is increasingly depleted of sodium with continued severe hyperglycemia, sodium is "drained" from the brain's intracellular compartment into the extracellular compartment and thence into CSF. Because of the ionic gradient, sodium may then move from CSF into serum to be lost via the kidneys. Brain tissue sodium decreases as a result of such flow. As a compensatory mechanism, intracellular sodium is replaced by potassium in order to maintain intracellular osmotic equilibrium as long as possible. The changes in the cellular membrane potential resulting from the changes in extracellular sodium and the intracellular movement of potassium could explain the cerebral dysfunction. The fact that this syndrome has been precipitated in man by diphenylhydantoin, which increased the extrusion of sodium from the cell /22,23/, adds credence to this postulated pathogenetic mechanism.

Finally, from McCurdy's review of various modes of treatment for this syndrome, it becomes apparent that the most successful treatment has been the inclusion of salt solutions into the therapeutic regimen. Replacement of sodium along with slow and gradual reduction of hyperglycemia should therefore be considered a major aspect of therapeutic management.

CONCLUSION

Rather than hyperosmolality, hyperglycemia, or hypernatremia, it appears that a disturbance in the ionic environment of the neuron resulting from total body sodium depletion is the key metabolic disturbance in hyperglycemic non-ketotic coma. It is hoped that this hypothesis will lead to more methodical studies of the CSF in patients with this syndrome.

References

1. Sament S, Schwartz MB: Severe diabetic stupor without ketosis. S Afr Med J 31:893-984, 1957
2. McCurdy DK: Hyperosmolar hyperglycemic non ketotic diabetic coma. Med Clin N Amer 54:683-699, 1970
3. Assan R, Souchal B, Aubert P, et al: Comas metaboliques non acido-cetiosiques chez les diabetiques. Presse Med 77:787-789, 1969
4. Davson H: Physiology of the cerebrospinal fluid. London:Churchill, 1967
5. Fishman RA: Carrier transport of glucose between blood and cerebrospinal fluid. Amer J Physiol 206:836-844, 1964
6. Tyler FH: Hyperosmolar coma. Amer J Med 45:485-487, 1968
7. Pickett WJ, Hirschowitz BI: Measurement of plasma osmolality. N Eng J Med 285:354-355, 1971
8. Maccario M: Neurological dysfunction associated with non ketotic hyperglycemia. Arch Neurol 19:525-534, 1968

9. Godeau T, Dorra M, Letac D, et al: Les comas par hyperosmolarite Presse Med 74:1297-1300, 1966
10. Arnaud P, Paille M, Paille J, et al: Le coma par hyperosmolarite chez les diabetiques Presse Med 79:949-1019, 1971
11. Labram C, Jacques G: Reflexions critiques sur le syndrome hyperglycemie avec hyperosmolarite et sans acidocetose. Presse Med 76:2145-2148, 1968
12. Espinas OE, Poser CM: Blood hyperosmolality and neurologic deficit. Arch Neurol 20:182-186, 1969
13. Earley LF, Daugharty TM: Sodium metabolism. N Eng J Med 281:72-86, 1969
14. DeRubertis FR, Michelis MF, Beck N, et al: "Essential" hypernatremia due to ineffective osmotic and intact volume regulation of vasopressin secretion. J Clin Invest 50:97-111, 1971
15. Johnson RD, Conn JW, Dykman CJ, et al: Mechanisms and management of hyperosmolar coma without ketoacidosis in the diabetic. Diabetes 18:111-116, 1969
16. Katzman R: Effect of electrolyte disturbance on the central nervous system. Ann Rev Med 17:197-212, 1966
17. Katzman R, Graziani L, Ginsburg S: Cation exchange in blood, brain and CSF. Progr Brain Res 29:283-296, 1968
18. Holliday MD, Kalayci MD, Harrah J: Factors that limit brain volume changes in response to acute and sustained hyper-and hyponatremia. J Clin Invest 47:1916-1921, 1968
19. Bradbury MWB, Kleeman CR: The effect of chronic osmotic disturbance on the concentration of cations in CSF. J Physiol 204:181-193, 1969
20. Wakim KG: Predominance of hyponatremia over hypo-osmolality in simulation of the dialysis disequilibrium. Mayo Clin Proc 44:433-460, 1969
21. Zierler KL: Hyperosmolarity in adults. J Chron Dis 7:1-21, 1958

22. Goldberg EM, Sanbar SS: Hyperglycemic, nonketotic coma following administration of Dilantin. Diabetes 18:101-106, 1969
23. Pincus JH, Rawson MD: Diphenylhydantoin and intracellular sodium metabolism. Neurology 19:419-422, 1969

NEUROLOGICAL MANIFESTATIONS OF ENDOCRINE DISEASES

Arnold H. Greenhouse, M.D.*

This paper discusses briefly the effects of endocrine disease on the peripheral and central nervous system. An equally important topic, that of central nervous system control of endocrine function, will not be covered herein. Greatest emphasis is given to disorders encountered most frequently by the clinician, particularly those of the thyroid and adrenal glands. There will be only scant mention of endocrine tumors, such as pituitary adenomas, since this presentation is concerned primarily with disordered neurological function secondary to hormonal secretions.

THYROID GLAND

HYPERTHYROIDISM

Myopathy

Acute thyrotoxic myopathy is a rare disorder with rapid progression, diffuse muscle weakness, bulbar palsy and a high mortality. Some workers doubt the existence of this condition, whereas other believe that most patients so diagnosed really have myasthenia gravis.

Chronic thyrotoxic myopathy is much more common than the so-called acute form of the disease. This disorder occurs more often in men than women, despite the greater frequency of thyrotoxicosis in the latter. This is a specific condition with d ıite myopathic electromyographic (EMG) changes which should ..ot be confused with the generalized weakness present in many thyrotoxic patients secondary to the catabolic effects of thyroid hormone. It is claimed that a myopathy universally accompanies hyperthyroidism, but this contention is disputed.

* Professor and Chairman, Department of Neurology, The University of New Mexico School of Medicine, Albuquerque

Without question there are thyrotoxic patients with striking focal weakness and wasting, an abnormal muscle biopsy, a myopathic EMG and markedly elevated serum values for creatine phosphokinase (CPK), serum glutamic oxalocetic transaminase (SGOT) and aldolase. Brisk deep tendon reflexes may occur, a finding which helps in eliminating some other muscle diseases. However, active reflexes also can be seen in polymyositis, which is the most frequent diagnosis to be considered when a myopathy appears in the adult.

Myasthenia Gravis

Considerable confusion exists over the relation between hyperthyroidism and myasthenia gravis and at present a definite position on this subject cannot be taken. Clinical experience indicates that the association is more than casual. It is said that from 3 to 6 percent of all myasthenic patients have thyrotoxicosis, whereas less than one percent of the latter develop myasthenia. The effects of having thyrotoxicosis on myasthenic patients is variable. In most instances, treatment of the thyroid condition improves the patient, but in some cases there is definite worsening. However, as a general statement, euthyroidism is the best state for the myasthenic whereas increased or decreased thyroid function can be expected to affect him adversely.

Periodic Paralysis

Periodic paralysis is definitely related to hyperthyroidism and in this condition almost all patients are males whereas in the familial variety, men predominate by a 3:1 ratio. The majority of patients are between 20 and 40 years of age, a somewhat older group than in familial hypokalemic periodic paralysis, but there is sufficient age overlap to prevent this distinction from being a diagnostic help. However, since familial periodic paralysis is generally a disorder of the young, the onset of this disease in middle age should raise the possibility of hyperthyroidism. In over 80 percent of patients with thyrotoxic periodic paralysis, the metabolic problem antedates the neurological disorder and a family history is definitely rare. The majority of patients reported with thyrotoxic periodic paralysis are Oriental, possibly reflecting the high carbohydrate diet in this group. Nonetheless, the condition occurs in all races, having been encountered in American Indians, Spanish-Americans and Caucasians. The production of iatrogenic thyrotoxicosis

in patients with familial periodic paralysis does not exacerbate their underlying condition, suggesting a different mechanism for hypokalemic paralysis in hyperthyroidism and in the familial disease. Periodic paralysis in thyrotoxicosis is associated with low rather than elevated serum potassium. Treatment consists of curing the hyperthyroidism, which usually results in a disappearance of the paralytic episodes.

Ophthalmoplegia

The basis for ophthalmoplegia in hyperthyroidism remains unknown, although it is suspected by some that the mucoprotein infiltration in the retro-orbital space responsible for the exophthalmos also produces the extraocular muscle paresis. The pathology consists of hypertrophic myositis and edema although myopathic changes also occur which are no different than in other varieties of thyrotoxic myopathy. In the majority of patients with thyrotoxic ophthalmoplegia, protrusion of the eye is also noted and in cases of malignant exophthalmos the movement paralysis may be secondary to muscle stretching. Many of these patients also experience an optic neuritis with visual impairment, which probably is mechanical in origin. Although LATS is suspected of playing a role in the genesis of exophthalmos, some controversy still exists as to this relationship and it may be of no importance in producing the ophthalmoplegia. Treatment is extremely difficult, and in many patients successful management of the thyroid disease may not affect either the ophthalmoplegia or the exophthalmos.

Effects of Hyperthyroidism on the Brain

Thyroid hormone is well-known to have many effects on the highest levels of brain activity. Among manifestations are emotional lability, anxiety, overreactiveness, tension, euphoria, depression and apathy. As in many disorders where disturbed metabolism produces psychological changes, their nature depends to some extent upon the patient's premorbid personality.

Thyroid storm is an unusual condition, much less common now than in the past, in which a thyrotoxic patient with a severe infection or following surgery develops severe generalized weakness, delirium, prostration and coma. In some instances there is bulbar paralysis, resembling botulism or poliomyelitis, an extremely serious situation which increases the already high death rate.

The electrical activity of the brain is modified by thyroid hormone. In normal man this substance increases the frequency of alpha rhythms, which is thought by some to be a direct action of thyroxine, although others feel that this is a nonspecific result of enhanced metabolism. In some animals, thyroxine lowers seizure threshold. When thyroid hormone is given to adrenalectomized rats, the effect is twice as great. The metabolic basis for thyroid hormone activity is believed to be a decrease in extracellular and an increase in intracellular sodium.

Spinal Cord in Hyperthyroidism

Occasionally, patients with hyperthyroidism show signs of spinal cord disease, with increased reflexes, extensor plantar signs, incontinence and even a sensory level. The major action of thyroid hormone in these cases seems to be a destruction of synaptic structures resulting from an unfavorable effect on spinal cord neuronal respiration. The resulting disturbance of oxygen metabolism causes increased vascular permeability and altered cerebrospinal fluid dynamics.

HYPOTHYROIDISM

Effects of Hypothyroidism on Muscles

A major manifestation of hypothyroidism is pseudomyotonia, a condition which is secondary to abnormalities of muscle contractile substance. The major clinical manifestation is delayed relaxation of deep tendon reflexes. Muscle biopsy shows vacuolization. Upon muscle percussion there often is a residual area of persistent abnormal contraction.

Patients with hypothyroidism may have clinically apparent myotonic syndromes although generally this disorder in myxedema is asymptomatic and found only by physical examination. The EMG reveals discharge potentials of increased duration and voltage as compared to those in true myotonia where they are repetitive but normal in appearance.

It is thought by some that a non-myotonic myopathy occurs in hypothyroidism, but clinical evidence to this point is lacking. Certainly, the florid proximal weakness, myopathic electromyographic changes and elevated serum enzyme levels, so common

in hyperthyroidism, are rarely seen in myxedema. Mucoprotein infiltration of muscles is probably responsible for the muscular abnormalities in myxedematous patients. Thyroid hormone is thought to affect the electrical activity of muscle by regulating the number of muscle fibers discharged with each impulse. Lack of this hormone may increase activity, possibly producing the myotonic-like picture seen in myxedema, whereas excess hormone may decrease the electrical discharges. If this theory is correct, then the neuromuscular disturbances in all thyroid disease may have one common denominator.

Effects of Hypothyroidism on Brain Function

The effects of thyroid hormone deficiency on the brain are well-known and particularly evident in cretinism. In this disorder, early treatment is vital to prevent mental deficiency, and even if the diagnosis is made immediately after birth normal mental development is rarely achieved. In contrast, childhood myxedema with onset after the neonatal period usually does not cause irreparable brain damage and adequate treatment may result in complete recovery.

In adult myxedema mental symptoms dominate the clinical picture. Among these are loss of interest and initiative, apathy, slowing of response, failing of memory and dulling of personality. Overt psychotic symptoms are common and often include mania, delusions, hallucinations and paranoia. To a large extent, the premorbid personality will determine these manifestations. The electroencephalogram (EEG) concomitant of myxedema is lowering of amplitude and slowing of rhythms. Increased levels of protein and of gamma globulin are found frequently in the spinal fluid. Myxedematous patients may have seizures, even if they did not have epilepsy previously.

A striking clinical picture, seen occasionally in hypothyroidism, is so-called "myxedema madness" which is in reality an accentuation of the mental symptoms described above, dominated by an overt psychosis. Such patients can be found in mental hospitals and at times they go unrecognized for prolonged periods.

Of ominous import is myxedema coma, a condition seen more commonly in females than in males (paralleling the sex incidence of myxedema). Although occurring in all age groups, patients

are more commonly in their sixties. Usually they have had chronic myxedema and then they present the clinical picture of coma developing under certain usually adverse circumstances such as extremely cold weather, infection, trauma or the administration of phenothiazine drugs. The mortality is in excess of 70 percent. The major clinical manifestations are progressive stupor followed by loss of consciousness, hypothermia, hypotension, tachycardia and slow shallow respiration. About 25 percent of these patients have generalized convulsions. It is thought that carbon dioxide narcosis plays a role. Immediate treatment is required urgently. Patients should be warmed, a rapidly acting thyroid hormone must be given and artificial respiration is occasionally applied. There is no proof that adrenal steroids are helpful.

Another neurological manifestation of hypothyroidism, usually not associated with other neurological signs, is a cerebellar syndrome manifested by intention tremor, limb ataxia and disequilibration.

The peripheral nervous system may be affected in myxedema. Patients on occasion complain of sensory loss of paresthesias. The EMG will show decreased nerve conduction velocities. Nerve biopsy reveals spreading apart of individual nerve fibers and basophilic metachromasia of the endoneurium and perineurium. Delayed relaxation of deep tendon reflexes is not secondary to peripheral nerve involvement, but, as pointed out above, has a muscular origin. A relatively common manifestation of peripheral nerve injury in myxedema is a carpal tunnel syndrome, which can be the initial manifestation of this disease and which usually subsides completely with successful hormone replacement therapy.

Cranial nerve involvement occurs in myxedema, with the eighth cranial nerve being affected most frequently. Deafness is said to be present in approximately 15 to 30 percent of myxedematous patients. Vestibular nerve dysfunction, with vertigo and tinnitus, also occurs. Occasionally, other cranial nerve deficits, such as facial palsy, are seen but this is distinctly less common.

The physiologic effects of hypothyroidism on the brain are, on the whole, unknown, although there is decreased cerebral blood flow and diminution of cerebral oxygen and glucose consumption. Oxidative phosphorylation by mitochondria is probably diminished. Alterations occur in the appearance of the ground substance of the brain and in protein metabolism.

ADRENAL GLANDS

ADDISON'S DISEASE

Psychiatric Symptoms

The incidence of psychiatric symptoms in this disease is 70 to 80 percent. Among these are dullness, apathy, irritability, negativism and confusion, all of which are, of course, indistinguishable from the psychological findings in other metabolic encephalopathies such as myxedema. Many patients become overtly psychotic, with paranoid delusions predominating. Agitation and disorientation are also frequent. Worsening of these symptoms is said to herald an Addisonian crisis.

Addisonian Crisis

The symptoms of Addison's disease intensify when a crisis is impending. Delirium is seen frequently, followed by convulsions, stupor and coma. The manifestations are so striking that a brain tumor is occasionally suspected. Rapid treatment is essential to prevent death.

Neurological Findings in Addison's Disease

Convulsions occur frequently, and some claim that they are independent of blood sugar levels, although hypoglycemia in this disorder is a frequent precipitant of seizures. Many patients with Addison's disease complain of numbness and tingling in the extremities, although the actual occurrence of peripheral neuropathy has not been studied adequately. It is known that synaptic transmission and central conduction rates are reduced in the adrenalectomized animal. In a few patients with adrenal insufficiency peripheral nerve conduction velocities are decreased.

Hyperkalemic periodic paralysis with flaccid quadriplegia occasionally occurs in Addison's disease, possibly due to a failure of adequate sodium exchange in the distal convoluted tubules. This picture must be distinguished from spinal cord disease due to Addisonism but if the paralysis is secondary to this latter cause there should be a sensory level and a spastic rather than flaccid quadriplegia.

Effects of Hypoadrenalism on the Brain

The EEG in Addison's disease is said to show diffuse high voltage slowing. These findings correlate roughly with the blood sugar level, despite the claim that seizures may occur independently of such concentrations. The central nervous system abnormalities in Addison's disease are probably secondary to disturbed electrolyte metabolism, with an increased intracellular sodium and decreased potassium. Cerebral blood flow and oxygen consumption are decreased in adrenalectomized animals, although such studies in Addisonian patients were said to show no changes. Certain cerebral symptoms in adrenal insufficiency are caused by hypoglycemia, decreased glycogen and reduced brain carbohydrate content as found in adrenalectomized animals. A decrease in brain gamma amino butyric acid (GABA) content also has been reported, which may be of clinical importance since this substance is said to serve as an inhibitory transmitter.

CUSHING'S DISEASE

Psychiatric Symptoms

Psychiatric symptoms occur in over 80 percent of patients with Cushing's disease. The most common manifestation is depression, although paranoia, confusion, disorientation, emotional lability, euphoria and memory deficits have been reported in some patients. These psychological disturbances resemble those which are due to steroid medication. Many individuals with Cushing's disease develop a marked organic psychosis, and as with myxedema, the diagnosis is not infrequently overlooked and the untreated patient is placed in a mental institution.

Approximately 30 percent of patients have headaches. A peripheral neuropathy of the Guillain-Barré variety is also seen. Seizures occur in four percent of cases and the EEG frequently shows moderate slowing. These findings resemble the EEG changes due to ACTH and other steroids. There often is a proximal myopathy in Cushing's disease. There also may be generalized fatigue and weakness, a metabolic effect independent of myopathic or neuropathic involvement. The basis for central nervous system abnormalities in hyperadrenalism probably is diminished intracellular sodium and decreased glucose oxidation. Cerebral blood flow, however, is unchanged.

ALDOSTERONISM

In patients with aldosteronism there can be tetany due to hypochloremic alkalosis. Hypokalemic periodic paralysis is also seen. The major neurologic manifestations, however, are due to hypertension, and individuals so affected often have severe headaches. The blood pressure elevation may eventually cause ischemic strokes, intracerebral hemorrhage, subarachnoid bleeding and hypertensive encephalopathy. The latter consequences are particularly true in patients with bilateral adrenocortical hyperplasia, whereas those with adrenal tumors tend to have only moderate blood pressure elevation and malignant hypertension is not seen in these cases.

ADRENOGENITAL SYNDROME

In patients with these disorders, psychological problems are common but supposedly they are related to sexual orientation and do not have endocrine origin. In some instances of this entity, Addisonian features appear and there may be major electrolyte imbalances leading to coma, convulsions and marked weakness. Hypertension also is seen in these patients.

PHEOCHROMOCYTOMA

In pheochromocytoma, the neurologic manifestations are usually secondary to hypertension. Occasionally, intracerebral hemorrhage occurs during a bout of marked blood pressure elevation. Patients with these tumors have a high incidence of central nervous system neoplasms, particularly gliomas and meningiomas.

PARATHYROID GLANDS

HYPOPARATHYROIDISM

Neurological Manifestations

The cardinal sign of hypoparathyroidism is tetany. Seizures also occur, but this is likely related to an underlying predisposition to seizures. It is well-known that epileptics are more susceptible to developing convulsions from hypocalcemia than normal persons who were previously healthy. The EEG in hypoparathyroidism shows paroxysmal slow activity, undoubtedly based on low calcium levels since the administration of this ion improves both the tracing and the convulsive state. Other findings include retinal hemorrhages and papilledema secondary to the hypocalcemia but frequently raising the possibility of a brain tumor. Skull x-rays may show calcifications in the basal ganglia. These are of unknown origin. Successful treatment does not improve the radiologic picture. Ataxia, chorea and a Parkinsonian-like picture are found on occasion, but these extrapyramidal symptoms are not necessarily associated with basal ganglia calcifications, nor do patients with these radiologic changes always have clinical manifestations. Rarely, there is dementia in association with this disease, although loss of intellect is more common with pseudohypoparathyroidism.

Psychiatric Manifestations

Patients with hypoparathyroidism have psychological findings which resemble those occurring in other endocrine disturbances of sufficient severity. Toxic delirium with delusions and hallucinations, excessive irritability, marked anxiety and emotional lability are reported.

Pseydohypoparathyroidism

This recessively inherited disorder is a primary renal defect in which the distal convoluted tubules fail in their response to parathyroid hormone secretion. Hypocalcemia and many of the clinical manifestations mentioned above are present. Mental retardation is a frequent concomitant of this condition as it is of so-called pseudo-pseudohypoparathyroidism. In the latter hypocalcemia does not occur.

HYPERPARATHYROIDISM

Neurological Manifestations

In patients with this disease, diffuse muscular weakness is common. There is hyporeflexia with loss of tone, and it is not unusual for dysphagia to occur. Pain is also frequent, but is generally localized to bone. Diffuse headaches, marked personality changes and generalized seizures have been reported. Stupor and then coma develop when serum calcium levels are above 17 mg/100 cc. In some long-standing cases dementia is said to occur. Elevated spinal fluid protein is found in cases with high serum calcium levels.

Psychiatric Manifestations

Confusion, delusions, hallucinations, severe depression and paranoia have all been seen in patients with hyperparathyroidism.

PITUITARY GLAND

There are relatively few direct endocrine effects of pituitary dysfunction on the central nervous system, and generally pituitary problems manifest themselves either because of a tumor with compression of nearby structures or because of "target organ failure." If there is endocrine insufficiency then the neurologic consequences mentioned in the preceding portions of this paper can be expected.

Pituitary Tumors

The literature on pituitary tumors is large and the neurologic consequences are complex. As already indicated, these will not be discussed in detail herein, but the primary and most important manifestations will be mentioned briefly.

Severe headaches are common, and when the tumor escapes from the sella turcica and impinges on nearby optic structures there will be visual field alterations, particularly bitemporal hemianopsia. Eventually there may be complete blindness. Papilledema, due to increased intracranial pressure, or optic atrophy are found in advanced cases. Cranial nerve palsies are produced by backward extension of the tumor. Invasion of the temporal lobe may cause seizures. The third ventricle may be entered by tumor mass, with consequent obstructive phenomena, increased intracranial pressure and loss of consciousness. Pituitary tumors causing acromegaly are somewhat smaller and produce fewer of the above problems than do the more common chromophobe adenomas. Acromegalic patients often are weak despite their increased muscle mass, and a carpal tunnel syndrome is not unusual in this state secondary to increase of tissues at the wrist.

Panhypopituitarism

This condition has a number of possible causes, including postpartum ischemic necrosis, destruction by an intrinsic tumor such as a chromophobe adenoma, aneurysms of the internal carotid artery and metastatic lesions. The manifestations may be those of the tumor itself as well as failure of various endocrine organs such as the adrenals, thyroid and gonads. An overriding symptom is weakness, but the other previously mentioned neurologic signs of endocrine insufficiency do occur. Confusion and various psychotic reactions are common. Acute pituitary failure in these patients, with coma and death precipitated by infections or trauma, represents a major medical emergency.

Effects of Specific Pituitary Hormones on the Central Nervous System

There are few well-documented and specific actions of various pituitary hormones on the central nervous system, and for the most part they act through the target endocrine glands. Growth hormone is said to increase the threshold for seizures.

Vasopressin produces a peripheral potentiation of sympathetic action. Thyrotopin also has a sympathetic stimulating effect, probably through a direct central (hypothalamic) effect.

SSI

Mind, *n.* A mysterious form of matter secreted by the brain. Its chief activity consists in the endeavor to ascertain its own nature, the futility of the attempt being due to the fact that it has nothing but itself to know itself with. From the Latin *mens*, a fact unknown to that honest shoe-seller, who, observing that his learned competitor over the way had displayed the motto "*Mens conscia recti*," emblazoned his own shop front with the words "Men's, women's and children's conscia recti."

Mine, *adj.* Belonging to me if I can hold or seize it.

Minor, *adj.* Less objectionable.

AMBROSE BIERCE, *circa 1880*
The Devil's Dictionary
(New York. Dover. 1958)

REMOTE EFFECTS OF CANCER ON THE NERVOUS SYSTEM

MAJ Garland E. McCarty, MC

Carcinoma with its remote effects has been shown to affect every organ system in the body in some manner. In the nervous system the remote effects cause pathological processes both proximally and distally, from the brain to the muscle. These conditions, therefore, will be presented in the following order:

BRAIN
- Progressive multifocal leukoencephalopathy
- Encephalomyelitis
- Subacute cerebellar degeneration

SPINAL CORD
- Encephalomyelitis
- Motor Neuron Disease

PERIPHERAL NERVE
- Neuromyopathy

NEUROMUSCULAR JUNCTION
- Lambert-Eaton syndrome

MUSCLE
- Neuromyopathy

Editor's Note:

The issue of the alleged remote effects of cancer on the nervous system remains a controversial one. There is little or no argument about the association of progressive multifocal leukoencephalopathy and Eaton-Lambert syndrome with malignancy. A growing body of neurologists has also accepted as valid the association of other entities with cancer as well, including encephalomyelitis, motor neuron disease, cerebellar degeneration and neuromyopathy. Opponents to this view assign the neurologic symptoms to malnutrition, specific dietary deficiencies, or to undiagnosed metastases. In many instances, postmortem data give little support as they are not available until after far-advanced metastatic disease has obliterated the original state in which the neurologic disease first appeared. Proponents point to the fact that the neurologic findings often precede discovery of the malignancy by many months. The great diversity of neurologic lesions tends to weigh against ascribing them solely to malnutrition. There are also a few autopsied cases in which no evidence of metastatic disease could be found to account for the neurologic problem.

The author has included the term "neuromyopathy" under categories for both peripheral nerve and muscle. Neuropathic or myopathic symptoms may predominate for a given patient, but often electromyographic evidence of both is present.

D.S.B.

BRAIN

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy was first described in 1958 by Astrom, Mancall and Richardson. Two cases were elderly women with chronic lymphocytic leukemia and the third a 42-year-old male with Hodgkin's disease. Progressive multifocal leukoencephalopathy occurring in chronic disease state is not common. Of forty-four cases reviewed by Richardson (1961), thirty-one (seventy percent) had some variety of neoplastic disease while nine (twenty percent) had some form of non-neoplastic granulomatosis or reticulo-endotheliosis. The other four patients (ten percent) had a pre-existing condition which could not be placed into either of these categories. TABLE I. The average age in Richardson's study was fifty-nine with the range from thirty-one to eighty-four years.

The neurological disorder progresses rapidly while the underlying disease may have been present many years. Typically, it has a course of three to six months from the onset of the first neurological changes to death (five days to just over one year in Richardson's series). The neurological symptoms and signs vary greatly but are usually asymmetrical. Hemiparesis evolving to quadraparesis, visual field defects or even blindness, aphasia, ataxia, dysarthria, dementia, confusional states, seizures and coma are the typical manifestations.

The cerebrospinal fluid, pneumoencephalograms, arteriograms, and brain scans are normal. The electroencephalogram (EEG) is abnormal (one exception has been reported by Hecker and Reid) and displays diffuse slowing.

The pathological picture consists of multiple foci of demyelination of various sizes

TABLE I

SUMMARY OF CASES OF NEOPLASTIC DISEASE (RICHARDSON'S STUDY)*

DISEASE	NUMBER OF CASES	TOTALS
Lymphoproliferative diseases		21
Chronic lymphocytic leukemia	9	
Hodgkin's disease	7	
Lymphosarcoma	4	
Plasmacytoma (multiple myeloma)	1	
Myeloproliferative diseases		7
Chronic myelocytic leukemia	3	
Acute myelocytic leukemia	1	
Polycythemia vera	3	
Non-neoplastic reticuloendotheliasis		9†
Sarcoidosis	5	
Tuberculosis	3	
Primary hypersplenism	1	
Whipple's disease	1	
Miscellaneous		7
Carcinomatosis	3	
Pulmonary anthracosilicosis	1	
Senility	1	
Senility; coronary heart disease; splenomegaly of uncertain cause	1	
Hepatosplenomegaly with liver and adrenal necrosis of uncertain cause	1	

*Richardson EP Jr. Progressive multifocal leukoencephalopathy. *New Eng J Med* 265:815-823, 1961
†One patient had both sarcoidosis and pulmonary tuberculosis

and stages of evolution. Lesions are found in the cerebral hemisphere, brain stem and cerebellum and have been reported in the spinal cord in three cases. Within these foci there are losses of myelin sheath with relative sparing of axons. There may also be some necrosis and disappearance of nerve cells in foci found in the deep layers of the cortex. In tissue surrounding the foci, bizarre densely basophilic oligodendroglia are found with eosinophilic intranuclear inclusions and loss of nuclear detail as well as giant cells with multiple nuclei or mitotic figures. Oligodendroglia are thought to give rise to the myelin sheaths during development of the central

nervous system and probably have an important part to play in maintaining the integrity of myelin the adult. Involvement of these cells may be primary to local breakdown of the myelin.

Despite the lack of inflammatory changes, the presence of inclusion bodies and the occurrence of this disorder in the course of systemic disease capable of interfering with immunological activity led Waksman and Adams to speculate that a virus infection might be implicated. Electron microscopy has shown virus-like particles in the glial cells. These virus-like particles are consistent morphologically with the virons of Papova virus, a group of viruses including the wart virus of man. The question is raised whether these virus-like particles could perhaps represent the reactivation or dissemination of a latent agent such as the wart virus or an as-yet-unknown human polyoma virus, or possibly represent a primary infection with a normally nonpathogenic agent.

Subacute Cerebellar Degeneration

Subacute cerebellar degeneration associated with carcinoma was first described by Greenfield in 1934. The clinical manifestations of this condition may precede the diagnosis of carcinoma by several months. The neurological findings include ataxia, dysarthria, nystagmus, cranial nerve palsies, mental changes, increased or decreased deep tendon reflexes and muscular weakness. Obviously more than just the cerebellum is involved. The pathological findings include a striking loss of Purkinje cells in the cerebellum with a narrowing of the granular cell layer, and some damage to the basket cells. Atrophy of the dentate nucleus or the inferior olives may be present along with degeneration of the ganglion cells of the ocular motor nuclei and other brain stem nuclei.

Degeneration of the spinocerebellar tracts (the direct spinocerebellar is more frequently involved), pyramidal tracts, the posterior columns and motor cells in the anterior horns is seen. Perivascular lymphocytic cuffing and partial demyelination of the white matter of the spinal cord may also be present.

In a review of seventeen cases by Lord Brain and Wilkinson, the age range for subacute cerebellar degeneration was from thirty-six to seventy years with the average age being 56.6 years. In nine cases the neoplasm was a lung carcinoma (including two of the oat cell type, three squamous, one adenocarcinoma, two undifferentiated carcinoma, and in one case the cell type was not known). There were five ovarian neoplasms, three adenocarcinoma, one an undifferentiated spheroidal-cell carcinoma, and in one the pathology was not known. Of the breast carcinomas one was a solid, travecular polygonal-cell carcinoma and in one the pathology was not known. The fallopian tube carcinoma was an adenocarcinoma. In ten of the seventeen, the presenting symptoms were those of the cerebellar lesion and in the remaining seven the initial symptom was that of the neoplasm. In the former the neurological symptoms appeared before the tumor by a period from two months to two years although in one case the cerebellar findings antedated the tumor by three years. In the latter cases the interval between the discovery of the tumor and the development of the neurological symptoms ranged between three months and two years.

The cerebrospinal fluid was examined in eleven cases. The cell count was normal in nine and increased in the other two (eleven and twenty cells/mm^3). The protein was normal in seven cases and increased in four (from 60-120 mg/100 cc).

SPINAL CORD

Encephalomyelitis with Carcinoma

This is a rare condition and only a few cases reported in the literature. It was originally described by Greenfield in 1934 under the title of "subacute cerebellar degeneration" in which he interpreted the inflammatory changes as reactive to degenerating nervous tissue. The most common tumor associated with this condition is oat-cell carcinoma of the lung but carcinoma of the breast and uterus are also reported. The lesion in the nervous system can be classified into four groups. TABLE II.

TABLE II

CLASSIFICATION OF MALIGNANT LESIONS IN NERVOUS SYSTEM

LESION	AREA LESION AFFECTS
Limbic encephalitis	Affects mainly the hippocampal formation, the amygdaloid nucleus, the cingulate and orbital cortex.
Bulbar encephalitis	Involves mainly the lower brain stem, and affects the substantia nigra, the inferior olives, perihypoglossal and vestibular nuclei, the dorsal vagal nucleus, spinal trigeminal nucleus, lateral cuneate nucleus, nuclei of the extra ocular muscles, dentate and subthalamic nuclei, and the nuclei of IX, X, XI, and XII.
Myelitis	Damages largely the anterior horn cells at varying levels, but also affects the other cell groups in some instances.
Ganglioradiculitis	Destroys the posterior root ganglia and causes Wallerian degeneration in the posterior columns and peripheral nerves

The neurological signs and symptoms may antedate the diagnosis of the neoplasm by many months or may appear after the diagnosis of the neoplasm. Clinical findings include mental changes, memory loss, vertigo, bulbar palsy, ophthalmoplegia, involuntary movements, nystagmus, ataxia, dysarthria, muscular weakness and wasting.

The pathological findings include lymphocytic infiltration in the meninges with extension into the perivascular spaces, microglial nodules and lymphocytic cuffing in the affected areas, loss of neurons, demyelination of various long tracts in the spinal cord, loss of myelin in the anterior nerve roots, loss of nerve cells in the dorsal root ganglia, Wallerian degeneration with fiber loss in the peripheral nerves and neurogenic atrophy of the muscles.

Carcinomatous Motor Neuron Disease

Amyotrophic lateral sclerosis (ALS), first described by Charcot and Jobbroy in 1869, is a chronic progressive disease of unknown etiology characterized by neurogenic atrophy of the somatic musculature. It is approximately twice as common in males as females and over eighty percent manifest the first sign of their disease in the fifth to seventh decades (forty to sixty years) with the average age being fifty-two years. It is a progressive disorder usually resulting in death within a few years of onset. The pathology consists essentially of a degeneration of the motor cells in the spinal cord, brain stem and to a lesser extent, in the cerebral cortex, with secondary degeneration of the fiber tracts in the lateral and ventral portions of the spinal cord.

Wechsler and his colleagues were the first to propose that ALS might be either primary (idiopathic) or symptomatic of some other disease. In thirteen cases of "symptomatic ALS" reported in 1944 they described one case of pancreatic carcinoma. Swank and Putnam, however, had described a case of ALS concurrent with a brain tumor in 1943. Norris and Engel in 1964 did a study of ALS and its association with neoplasms and then compared this to a series of stroke

patients which were collected nearly concurrently. They collected one hundred and thirty cases of ALS and found thirteen major neoplasms (ten percent) and two "minor" neoplasms. Proof that the neoplasm did not produce the clinical findings of ALS by invasion of the nervous system was obtained at autopsy in eight cases. Typical pathological findings of ALS were present in each autopsied case. There were few clinical differences between the ALS patient with and without cancer except that those with cancer were older at the onset of ALS and tended to be males.

Among the three hundred and twelve patients there were five instances of major neoplasm (1.6 percent) and one minor neoplasm in another patient. Since the average age in the entire stroke series was greater (sixty-two years) and there were more females than in the ALS series, a subgroup of stroke patients was obtained by systematically deleting the oldest females from the original stroke series until two hundred patients remained in a subgroup having age and sex characteristics more like the ALS series. Major neoplasms were found in two patients (1.0 percent).

In five of the thirteen cases, the ALS symptoms antedated the carcinoma from one to three years while they occurred at approximately the same time in another five cases. Successful cancer treatment was achieved in seven cases. Surgical removal of four well localized tumors, adequate radiation of another, surgery plus radiation of another and chemotherapeutic control of a case of leukemia all failed to alter the downhill course of ALS. This could mean that either traces of the neoplasm still existed or the neoplasm induced a lasting change. There has been a report of four cases of "progressive muscular atrophy" which were arrested after removal of pancreatic adenomas. In these cases the atrophy was thought to be due to hyperinsulinism.

An ALS-like picture has also been reported in lymphosarcoma, carcinoma of the thymus, basal cell carcinoma, adenocarcinoma of the prostate, colon and breast, and seminoma.

From 1953-1963 in the London Hospital nine-one cases of ALS were recorded and a neoplasm was present in five for an incidence of approximately six percent. In a study at the same hospital which included the above five cases, twelve cases of ALS were recorded in which there was a definite association of a neoplasm. Of these, eight were men and half of the neoplasms were carcinoma of the lung. Six presented initially with neurological symptoms from two months to five years before the neoplasm was discovered.

PERIPHERAL NERVE AND MUSCLE

Carcinomatous Neuromyopathy

Carcinomatous neuromyopathy includes a group of nonmetastatic clinical disorders of the neuromuscular system in patients with various malignant diseases. The incidence of carcinomatous neuromyopathy is variable depending upon the criteria for diagnosis. Croft and Wilkinson in a survey of 1,476 patients with cancer found an incidence of seven percent irrespective of the site of the neoplasm. When considering malignancies of the lung alone, the incidence was sixteen percent. They included any neurological abnormality such as weakness, decreased tendon reflexes, any sensory change. Other investigators have placed the percentage between 3.5-7.0 percent.

Although recognized for over two decades, classification of these syndromes remains difficult because the clinical pictures are varied and the pathology is not typical of either a neuropathy or of a myopathy. The classification given in TABLE III is the one generally accepted.

TABLE III

CLASSIFICATION OF CARCINOMATOUS SYNDROMES

Pure sensory neuropathy (ganglioradiculitis)
Peripheral sensorimotor neuropathy
Mild terminal neuropathy - those neuropathies found after the diagnosis of a neoplasm has been established and which plays no significant part in the patient's symptomatology.
Subacute neuropathy
Remitting and relapsing neuropathy

Sensory neuropathy associated with bronchogenic carcinoma (Denny-Brown, 1948) is characterized by loss of all sensory modalities particularly in the limbs, ataxia, and pseudo-athetosis. The neuropathy precedes the diagnosis of carcinoma in over sixty percent of the cases by a mean duration of six months (1-21 months). In a study by Croft and Wilkinson of eleven patients with such an entity, nine were female and nine had carcinoma of the lung, one had carcinoma of the esophagus and one had carcinoma of the cecum. In this condition there is a disproportionate number of females and a high incidence of lung carcinoma. The course is subacute, over a period of several months and may be disabling. The cerebrospinal fluid protein (CSF) is frequently elevated. Pathological specimens reveal extensive destruction of the posterior root ganglia with lymphocytic infiltration and Wallerian degeneration of the posterior columns. Mild inflammatory changes are frequently seen in the limbic cortex, the medulla oblongata or the spinal cord. Because of the pathological findings, it is suggested that this type of

sensory neuropathy and the encephalomyelitic form of carcinomatous neuropathy form a single entity. Investigation by Croft and his colleagues in 1965 revealed the presence of circulating organ-specific anti-brain antibodies in both the sera and the CSF.

In mild terminal neuropathy, the lung is the most common site of the neoplasm although it has been seen with carcinoma of the stomach and breast.

The subacute neuropathy form is seen more frequently in males. It is more common in lung carcinoma (approximately seventy-five percent) although it has been reported in multiple myeloma and reticulum cell sarcoma and carcinoma of the colon, bladder, and pancreas. The average age of onset is approximately sixty-three years and it precedes the diagnosis of carcinoma in over fifty percent of the cases by a mean interval of twenty-two months.

Remitting and relapsing sensorimotor neuropathy is more frequent in males, the mean age of onset is fifty-six years and is seen as frequently in neoplasm outside of the lung as in carcinoma of the lung (Hodgkin's disease, thymoma, seminoma, carcinoma of the breast, stomach and uterus and cervix). It is characterized by remissions and exacerbations and is diagnosed before identification of the neoplastic condition in only thirty percent.

Abnormalities in carcinomatous neuromyopathy include primarily axonal degeneration with late segmental demyelination and secondary muscle atrophy. In some cases histological changes characteristic of a myopathic process are seen.

Death in all of the neuromyopathies is usually due to the carcinoma.

Shy and Silverstein in 1965 studied one hundred and fifty-one patients, who presented with proximal muscle weakness. Of these twenty-seven had a remote malignancy (18.5 percent). Over the age of fifty there were sixty-nine patients, forty-four of whom were women and twenty-five men. Twenty-two of these patients had some type of malignancy (33.4 percent). Of the twenty-five men, fifteen had a remote malignancy (60 percent) and of the forty-four women, seven had a malignancy (18.25 percent).

NEUROMUSCULAR JUNCTION

Lambert-Eaton Syndrome

This condition is characterized by muscle weakness with easy fatiguability associated with carcinoma of the bronchus, usually of the oat-cell type. It was first mentioned by Anderson in 1953. More extensive studies with electromyographic (EMG) evidence of a defect in neuromuscular transmission was carried out by Lambert, Eaton and Rooke in 1956. This condition is also known as atypical myasthenia gravis, pseudomyasthenia, and myasthenic-myopathic syndrome.

The principal clinical characteristics have been weakness and easy fatiguability of the proximal muscles, particularly the pelvic girdle and thighs; weak or absent muscle stretch reflexes; relatively poor response to reostigmine but marked sensitivity to tubocurarine; and in many muscles an appreciable delay in development of strength at the onset of a maximal voluntary contraction. The principal features of the defect in neuromuscular transmission have been a marked block of transmission in rested muscle with facilitation upon activity.

In a series of thirty patients with this syndrome studied by Lambert and Rooke, none

presented with complaints of a thoracic tumor (twenty-two had or subsequently developed intrathoracic tumors). In fifteen the tumor was found during the initial clinic visit, in seven it was found seven to twenty-seven months after the diagnosis of myasthenic syndrome had been established. This syndrome is most frequently seen in oat-cell carcinoma of the lung and has not been reported in carcinomas outside the lung. The incidence has been estimated to be less than one percent of the number of patients with cancer of the lung but about six percent of the number with oat cell carcinoma.

The most decisive information for identifying the Lambert-Eaton Syndrome is provided by the response of a muscle to maximal electrical stimulation of its nerve. The action potential and twitch evoked in a rested muscle by a single maximal stimulus are greatly reduced in amplitude even though the strength of voluntary contraction may be normal or nearly so. Repetitive stimulation of the nerve at a slow rate (two shocks/sec) produces a further decrease in amplitude of the action potential and twitch which is progressive for the first few responses. However, during stimulation at fast rates (10-200 shocks/sec) a progressive increase in response occurs. The increase occurs at rates of stimulation comparable to the rate of impulses in motor neurons during strong voluntary contraction (20-40/sec). Thus, facilitation of the response during repetitive excitation accounts for the fact that strength of voluntary contraction may be normal even though the strength of a single twitch of the rested muscle is greatly reduced. The defect resembles that produced by magnesium, neomycin and votulinum toxin, agents which diminish release of acetylocholine from motor nerve endings. The effect of adequate tumor therapy on this condition is inconclusive although some patients have improved temporarily with removal of the tumor or with radiotherapy or chemotherapy.

OTHER CONDITIONS ASSOCIATED WITH NEOPLASMS
Waldenstrom's Macroglobulinemia

Approximately twenty-five percent of the patients with macroglobulinemia have neurological complications (Longothetis et al, 1960) which may be classified as encephalopathies, peripheral neuropathies, strokes and subarachnoid hemorrhages. Many of the manifestations of Waldenstrom's macroglobulinemia are secondary to increased serum viscosity and high macroglobulin levels. The retinopathy and visual disturbances, hemorrhagic diathesis, erythrocytic survival and congestive heart failure may be improved by plasmapheresis. The association of macroglobulinemia and neurological disease has been recognized as a clinical entity since 1936 (Bing-Neel Syndrome).

The retinopathy seen in this condition is manifested by venous distention, papilledema, retinal or vitreous hemorrhages and exudates, blurred vision, progressive visual loss and sludging of blood in the vessels. All of these findings are secondary to hypervicosity. Other manifestations include seizures and strokes (secondary to hypervicosity), headaches, coma, tinnitus, vertigo, decreased auditory acuity (probably secondary to vascular lesions in the cochlear and vestibular apparatus), nystagmus, hyperreflexia, and postural hypotension. There is also a bleeding tendency due to interference of the macroglobulins with various coagulation factors. The hearing loss, pyramidal tract signs and peripheral neuropathy are not directly related to serum vicosity. The cause for these conditions are unknown but gamma macroglobulins, as well as other gamma globulins, have been shown to have antibody activity and possibly these proteins are autoantibodies to antigens present in the nervous tissue (autoimmune mechanism).

Most workers have considered that the neurological aberrations result from either localized lymphomatous tumors or more commonly perivascular infiltrations of lymphocytoid plasma cells in the brain, meninges, spinal cord, or peripheral nerves. Evidence for the local production of macroglobulins by these cells is the finding of intranuclear and intracytoplasmic PAS-positive material which is thought to represent the carbohydrate-rich macroglobulin. However, the significance of these perivascular infiltrations is difficult to assess in that they have also been found in the brain and meninges.

Proteinaceous PAS-positive material has been noted within cerebral blood vessels and Virchow-Robin spaces. This finding, associated with coma, has been described as coma paraproteinemicum. The high serum viscosity may lead to vascular stasis and anoxemia.

Dermatomyositis

Dermatomyositis, a condition characterized by a rash and weakness, is frequently associated with neoplasms. Williams found that 9? of 590 cases of dermatomyositis reported in the literature were associated with malignancy (15.6 percent). Approximately half the cases of dermatomyositis occur before the age of forty. The incidence of associated tumors is higher in the older age group. In a report from the Cleveland Clinic (Arundell et al, 1960) more than half of dermatomyositis patients older than the age of forty had a neoplasm. The diagnosis of dermatomyositis may antedate the diagnosis of the tumor by many months.

Myasthenia Gravis

Myasthenia gravis is associated with a thymoma in approximately fifteen percent of

the patients. The symptoms of myasthenia are the presenting complaint in the majority of cases (fifty-one in fifty-six cases in Perso, Schwab and Castleman's series). In fifty-seven percent the interval was greater than one year before a thymoma was discovered. The thymoma may be benign or malignant.

References

Anderson HJ, Churchill-Davidson HD, Richardson AT: Bronchial neoplasm with myasthenia. Lancet 2:1291, 1953

Arundell FD, Wilkinson RD, Heserick JR: Dermatomyositis and malignant neoplasms in adults. Arch Derm 82:772, 1960 (Report from Cleveland Clinic)

Astrom KE, Mancall EL, Richardson EP Jr: Progressive multifocal leukoencephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. Brain 81:93, 1958

Bing J, Neel AV: Two cases of hyperglobulinemia with affection of the central nervous system on a toxi-infectious basis. Acta med scand 88:492, 1936

Brain, The Lord, Croft PB, Wilkinson M: Motor neurone disease as a manifestation of neoplasm. Brain 88:479, 1965

Brain, The Lord, Norris FH Jr (eds): The Remote Effects of Cancer on the Nervous System. New York: Grune and Stratton, 1965

Brain, The Lord, Wilkinson M: Subacute cerebellar degeneration associated with neoplasms. Brain 88:465, 1965

Croft PB, Henson RA, Urich H, et al: Sensory neuropathy with bronchial carcinoma. A study of four cases showing serological abnormalities. Brain 88:501, 1965

Croft PB, Urich H, Wilkinson M: Peripheral neuropathy of sensorimotor type associated with malignant diseases. Brain 90:31, 1967

Croft PB, Wilkinson M: The course and prognosis in some types of carcinomatous neuromyopathy. Brain 92:1, 1969

Croft PB, Wilkinson M: The incidence of carcinomatous neuromyopathy with various types of carcinoma. Brain 88:427, 1965

Dayan AD, Croft PB, Wilkinson M: Association of carcinomatous neuromyopathy with different histological types of carcinoma of the lung. Brain 88: 435, 1965

Denny-Brown D: Primary sensory neuropathy with muscular changes associated with carcinoma. J Neurol Neurosurg Psychiat 11:73,1948

Greenfield JG: Subacute spinocerebellar degeneration occurring in elderly patients. Brain 57:161, 1934

Hecker R, Reid RT: Cerebral demyelination in Whipple's disease. Med J Australia 49(1):211 (10 Feb) 1962

Henson RA, Hoffman HL, Urich H: Encephalomyelitis with carcinoma. Brain 88:449, 1965

Lambert EH, Eaton LM, Rooke ED: Defect of neuromuscular conduction associated with malignant neoplasms. Amer J Physiol 176:612, 1956

Lambert EH, Rooke ED: Myasthenic state and lung cancer. IN The Remote Effects of Cancer on the Nervous System. Contemporary Neurology Symposia. Vol I. Brain, The Lord, Norris FH (eds). New York: Grune and Stratton, 1964. pp 67-80

Logothetis J, Silverstein P, Coe J: Neurologic aspects of Waldenström's macroglobulinemia. Report of a case. Arch Neurol 3:564, 1960

Norris FH, Engel WK: Neoplasms in patients with amyotrophic lateral sclerosis. Trans Amer Neurol Ass 89:238, 1964

Norris FH Jr, Kurland LT (eds): Motor Neuron Diseases. New York: Grune and Stratton, 1967

Perlo VP, Schwab RS, Castle B: Myasthenia gravis and thymoma. IN The Remote Effects of Cancer on the Nervous System. Contemporary Neurology Symposia. Vol I. Brain, The Lord, Norris FH (eds). New York: Grune and Stratton, 1964. pp 55-66

Richardson EP Jr: Progressive multifocal leukoencephalopathy. New Eng J Med 265:815, 1961

Shy GM, Silverstein I: A study of the effects upon the motor unit by remote malignancy. Brain 88:515, 1965

Swank RL, Putnam TJ: Amyotrophic lateral sclerosis and related conditions. Arch Neurol Psychiat 49:151, 1943

Trojaborg W, Frantzen E, Anderson I: Peripheral neuropathy and myopathy associated with carcinoma of the lung. Brain 92:71, 1969

Waksman BH, Adams RD: Infectious leukoencephalitis. A critical comparison of certain experimental and naturally occurring viral leukoencephalitides with experimental allergic encephalomyelitis. J Neuropath Exp Neurol 21:491, 1962

Wechsler IS, Sapirstein MR, Stein A: Primary and symptomatic amyotrophic lateral sclerosis. Amer J Med Sci 208:70, 1944

Williams RC Jr: Dermatomyositis and malignancy. A review of the literature. Ann Intern Med 50:1174, 1959

Wilkinson PC, Zeromski J: Immunofluorescent detection of antibodies against neurones in sensory carcinomatous neuropathy. Brain 88:529, 1965

SPECTRUM OF VIRUS INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

MAJ William James Curtin, MC

The word VIRUS is derived from the Latin and Greek terms for poison or stench, akin to the noxious gas arising from the marshes. Viruses are agents made up of nucleic acid, either DNA or RNA, interwoven with or surrounded by a surface crystal called a capsid. Viruses can only reproduce inside living cells and within living cells they direct the cell's synthetic machinery toward the manufacture of specialized particles, the virions, which exist as vehicles for the transmission of viral nucleic acid from cell to cell. The introduction of this new genetic material into susceptible host cells can induce these cells to produce viral components and assemble virus particles that are then capable of further cell-to-cell transmission.

The concept of virus as a cause of disease is ancient, but the actual nature of these agents is only now becoming fully appreciated. At the beginning of this century when viruses were first being propagated in the laboratory, it was found that they passed through filters that held back bacteria and that they failed to grow except within living cells. Shortly afterward, it was found that they require special media for artificial cultivation but survive for long periods in glycerol and in the dry state. Viruses are destroyed by heat at relatively low temperatures, but are resistant to cold. They are more susceptible to oxidizing agents, such as hydrogen peroxide and potassium permanganate, than to ordinary disinfectants.

The taxonomy of viruses has been a troublesome area for many years. Some viruses have been

classified by their site of growth (enteroviruses, rhinoviruses), others by common antigens (adenoviruses, poxviruses), and still others by ecological characteristics (arthropod-borne viruses). The present trend to classify by morphological or physiochemical properties is probably not as satisfactory as the traditional nomenclature because viruses are proving to have many similar morphological and physicochemical properties.

Virus Infections of the Central Nervous System (CNS)

The term "neurotropic virus" is commonly used to describe the minute filterable pathogenic agents which are invisible by light microscopy and range in size from 125 μ in the case of rabies and lymphocytic choriomeningitis to 10-25 μ in the case of poliomyelitis and equine encephalitis. It is not their invisibility to light microscopy nor their approximate size which distinguishes neurotropic viruses but the fact that they have a cell type specificity, or more accurately, a more marked affinity for certain tissues within the nervous system. This affinity of the neurotropic visuses is, in general, for the grey matter of the nervous system; hence they have been called polioclastic.

The central nervous system can be attacked by many different viruses but the following clinical features are common to most:

There is a generalized viremia, which, in a proportion of cases is followed by localization in the central nervous system.

The virus may predominately involve..

Brain - viral encephalitis, e.g. mumps encephalitis or herpes simplex encephalitis

Meninges, e.g. lymphocytic choriomeningitis

Spinal cord - myelitis, e.g. poliomyelitis

> The virus multiplies within the central nervous system tissues, which, as a result, shows changes varying from reversible degeneration to irreversible necrosis.

Although there is a tendency on the part of clinicians to divide virus infections of the nervous system into distinct syndromes(such as encephalitis versus aseptic meningitis), it is important to emphasize that often there is no clear-cut distinction.

The pathologic picture in viral encephalitis includes destruction or damage to neurons, the presence of intranuclear inclusion bodies, and edema and inflammation of the brain and spinal cord with perivascular cuffing by polymorphonuclear leukocytes and lymphocytes. There is an angiitis of small blood vessels, with thrombosis, and proliferation of astrocytes and microglia. There may also be widespread white matter destruction by the inflammatory process and by thrombosis of perforating vessels. The pathology in aseptic meningitis is that of meningeal and choriod plexus inflammation, with marked hyperemia and lymphocyte infiltration.

Turning from the relatively acute viral central nervous system infections, I would now like to describe briefly another area of increasing importance in the spectrum of central nervous system viral infections — the slow and chronic virus infections. The concept that viruses can cause diseases with long incubation periods, episodic or chronic disease, and disease with varied pathologic reactions is not new, e.g., long incubation periods of rabies, or the chronicity and noninflammatory neoplastic pathology of warts. What is new is a resurgence of interest in viruses as possible causes of relapsing, subacute or chronic neurological disorders of man. The many recent observations of both virologists and morphologists of the

relationships of a variety of viruses to human neurological diseases include the elucidation of the chronic nature of rebella infection of the fetus and newborn, the newer theories of the pathogenesis of herpes zoster, the repeated electron microscopic observation of virus-like particles in progressive multifocal leuko-encephalopathy and in subacute sclerosing panencephalitis, and the transmission of kuru and Jakob-Creutzfeldt diseases to chimpanzees.

These diverse and preliminary observations do not yet allow dramatic conclusions but they do provide a vista of future possibilities.

TABLES I through V are summations of some of the pertinent facts on the various viruses which have been documented or have been strongly postulated on the basis of our current knowledge. The condensation of this material into tabular form will hopefully allow for greater appreciation of the spectrum of virus infections of the central nervous system.

TABLE I

PATHOGENESIS OF VIRUS INFECTIONS OF THE CENTRAL NERVOUS SYSTEM

VIRUSES	PORTAL OF ENTRY OF HUMAN NEUROPATHOGENS
Rabies and B-virus	Inoculation
Arthropod-borne	Animal bite Mosquito or tick bite
Mumps, lymphocytic choriomeningitis, and herpes simplex	Respiratory
Poliomyelitis, coxsackie and echo	Enteric
Rubella and cytomegaloviruses	Transplacental

TABLE II

PATHWAYS OF SPREAD OF VIRUSES TO THE CENTRAL NERVOUS SYSTEM (CNS) IN HUMANS

PATHWAY OF SPREAD TO CNS	VIRUSES IN MAN (Probable)
NEURAL	Rabies, B-virus, possibly poliomyelitis
OLFACTORY	Possibly herpes simplex in adults
HEMATOGENOUS	Poliomyelitis, coxsackie, echo, lymphocytic choriomeningitis, mumps; herpes simplex in children; rubella and cytomegaloviruses in fetuses

TABLE IIIA.

ETIOLOGY OF ACUTE VIRAL CNS INFECTIONS*

ETIOLOGIC AGENT	WAIR STUDY† (1953-1958) Percent of Cases
MUMPS	16
LYMPHOCYTIC CHORIOMENINGITIS	14
ARTHROPOD-BORNE VIRUSES	14
HERPES SIMPLEX	10
ENTEROVIRUSES	8
LEPTOSPIROSIS	2

**Definition of Encephalitis.* Acute illness with severe or moderate depression of consciousness, seizures, and/or focal neurologic signs (other than those of poliomyelitis) plus cerebrospinal fluid pleocytosis and bacteriologically sterile cerebrospinal fluid.
†Excerpt from Meyer HM Jr, Johnson RT, Crawford JP, et al: Central nervous system syndromes of "viral" etiology. A study of 713 cases. *Amer J Med* 29:334-347, 1960. Study conducted by group at Walter Reed Army Institute of Research (WAIR).

TABLE IIIB

ETIOLOGY OF ACUTE VIRAL CNS INFECTIONS*

ETIOLOGIC AGENT	WAIR STUDY† (430 cases)	CLEVELAND STUDY‡ (420 cases)
	percentage	
ENTEROVIRUSES	30	45
Poliomyelitis	9	7
Coxsackie (Primary) (Group B)	18	24
Echo	12	14
Mumps	16	6
LYMPHOCYTIC CHORIOMENINGITIS	19	...
LEPTOSPIROSIS	4	...
HERPES SIMPLEX	1	...
ARTHROPOD-BORNE VIRUSES	1	...
OTHER	2§	3‖

**Definition of Aseptic Meningitis.* Acute febrile illnesses with nuchal rigidity, cerebrospinal fluid (CSF) pleocytosis, and bacteriologically sterile CSF, and without focal signs or sequelae.

†Excerpt from Myer HM Jr, Johnson RT, Crawford JP, et al: Central nervous system syndromes of "viral" etiology. A study of 713 cases. *Amer J Med* 29:334-347, 1960

‡From Lepow MD, Carver DH, Wright FT Jr, et al: A clinical, epidemiologic and laboratory investigation of aseptic meningitis during the four-year period, 1955-1958. *New Eng J Med* 266:1181-1187, 1962

§Includes infectious mononucleosis, primary atypical pneumonia, Rocky Mountain spotted fever, and mycotic infections

‖Mixed infections -- either two enteroviruses or enteroviruses and mumps

TABLE IV

COURSE OF ENCEPHALITIS*

PROGNOSIS	TOTAL PATIENTS	COMPLETE RECOVERY	SEVERE SEQUELAE	DEATH
Mumps	22	21	1	...
Lymphocytic choriomeningitis	20	19	1	...
Arthropod-borne viruses	20	11	6	3
Herpes simplex	13	2	6	5

*Excerpt from Myer HM Jr, Johnson RT, Crawford JP, et al: Central nervous system syndromes of "viral" etiology. A study of 713 cases. *Amer J Med* 29:334-347, 1960

TABLE V

SUBACUTE OR CHRONIC HUMAN DISEASES OF THE NERVOUS SYSTEM KNOWN OR SUSPECTED TO BE OF VIRAL ETIOLOGY

Infectious Virus Demonstrated

Kuru
Chronic arbovirus encephalitis
  Kozhevnikov's epilepsy or chronic Russian spring-summer encephalitis with epilepsia partialis continua
Creutzfeldt-Jakob disease
  subacute spongiform encephalopathy or subacute presenile polioencephalopathy
? Vilyuisk encephalitis
?? Subacute sclerosing panencephalitis (Dawson's encephalitis)

Viral Antigens or Virus-like Structures Demonstrated

Subacute sclerosing panencephalitis
Progressive multifocal leukoencephalopathy

Virus not Demonstrated

Postulated on Histopathological or Epidemiological Grounds (without direct or indirect demonstration of virus)

Encephalitis lethargica (von Ecomomo's encephalitis)
Presenile dementia's (Alzheimer's and Pick's diseases)
Progressive cerebral poliodystrophy (Alper's disease)
Amyotrophic lateral sclerosis and the amyotrophic lateral sclerosis -- parkinsonism -- dementia complex of Guam
Multiple sclerosis
Leukodystrophies (Schilder's and Krabbe's disease)

References

Bang FB, Luttrell CN: Factors in pathogenesis of virus diseases. Advances Virus Res 8:199-244, 1961

Fenner F: The Biology of Animal Viruses. New York: Academic Press, 1968 (two volumes)

Gajdusek DC: Slow virus infections of the nervous system. New Eng J Med 276:392-400, 1967

Gajdusek DC, Gibbs CJ Jr, Alpers M: Transmission and passage of experimental "kuru" to chimpanzees. Science 155:212-214, 1967

Gibbs CJ Jr, Gajdusek DC, Asher DM, et al: Creutzfeldt-Jakob disease (spongiform encephalopathy) transmission to the chimpazee. Science 161:388-389, 1968

Gibbs CJ Jr: Search for infectious etiology in chronic and subacute degenerative diseases of the central nervous system. Current Topics Microbiol 40:44-58, 1967

Horsfall FL, Tamm I: Viral and Rickettsial Infections of Man, 4th edition. Philadelphia: Lippincott, 1965

Johnson RT, Mims CA: Medical Progress. Pathogenesis of virus infections of the nervous system. New Eng J Med 278:23-30 and 84-92, 1968

Lepow MD, Carver DH, Wright HT Jr, et al: A clinical, epidemiologic and laboratory investigation of aseptic meningitis during the four-year period, 1955-1958. New Eng J Med 266:1181-1187, 1962

Luria SE, Darnell JE: General Virology. New York: John Wiley, 1967

Meyer HM Jr, Johnson RT, Crawford JP, et al: Central nervous system syndromes of "viral" etiology. A study of 713 cases. Amer J Med 29:334-347, 1960

SOME AUTOSOMAL CHROMOSOME ABNORMALITIES

MAJ William Stroud Connor, MC

The recognition that certain syndromes were due to chromosomal abnormalities was delayed for many years by a mistaken impression regarding the normal number of human chromosomes. Painter studied testicular tissue from three convicts and initially reported in 1921 that his clearest plates showed 46 chromosomes, with a range from 45 to 48. Unfortunately, when his final report was published in 1923, he had decided that 48 was the actual human chromosome complement. Thus when Mittwoch in 1952 reported on her study of spermatogenesis in a mongoloid, she described 24 rather than 23 chrosomal masses during the first stage of meiosis, but, because of Painter's work, she failed to appreciate that this was abnormal. It was not until 1956 that Tjio and Levan shook the foundations of genetics by pointing out that there were really only 46 human chromosomes normally. They used an improved cytologic technique described by Hsu in 1952. Ironically, some of Hsu's original plates actually showed 46 rather than 48 chromosomes. Yet it was asserted that his plates all showed 48 chromosomes, suggesting the effect on perception of commonly held fallacies. After Tjio and Levan's radical correction, the recognition of chromosomal abnormality syndromes began proceeding at a rapid rate. In 1959 Lejeune and colleagues discovered 47 chromosomes in each of three patients with mongolism, with the additional chromosome being in the "G" group, which consists of chromosomes Nos. 21 and 22. Then the phenomenon of "translocation", which refers to a part of one chromosome becoming attached or translocated to another chromosome followed by replication of both portions of

chromosomal material as a single unit, was discovered. For example, if a portion of a G-group chromosome becomes attached to a chromosome of the D-group, consisting of chromosomes Nos. 13, 14, and 15, the result may be referred to as D/G translocation. In 1960, in quick succession, the first D/G translocation, the first G/G translocation, and the first familial transmission (parent to child) of translocation in mongolism were reported. And in 1961 the first report of mosaicism for trisomy G appeared — that is, an individual was found whose body was comprised of two different cell lines. Some cells had a normal chromosomal complement, 46, and other cells contained 47 chromosomes. Subsequently new innovations in technique have permitted further clarification of chromosomal abnormality.

The use of tritiated thymidine in cell culture has permitted differentiation among chromosomes in various groups according to their rate of replication. If tritiated thymidine is added to cell culture shortly before stopping replication in metaphase with colchicine, only those chromosomes that replicated late, i.e. only a short while before metaphase, will show uptake of tritiated thymidine. If a longer incubation period is permitted with tritiated thymidine before adding colchicine, then early replicating chromosomes will also show uptake. By this method the chromosomal abnormality in, for example, cri du chat ("cry of cat") syndrome was more clearly defined. It had been shown that this syndrome involved partial deletion of chromosomal material in the B group, consisting of chromosomes Nos. 4 and 5. The tritiated thymidine technique showed the partial deletion to involve that chromosome which replicates the earlier of the two — No. 5. But neither this technique nor simple inspection was able to distinguish adequately between chromosomes No. 21 and 22. And so the

An increased incidence of thyroid abnormalities among mothers of mongols has led to antithyroid antibodies being suggested as agents interfering with normal disjunction of chromosomes.

Recognition of older mongols is comparatively easy. The pleasant babbling mentally retarded child with flattened face and occiput, short stature and waddling gait, small rounded ears, eyes with oblique palpebral fissures and obvious epicanthal folds, and perhaps a protruding tongue, is a quick "gestalt" street diagnosis. Babies are not as easy to recognize. In addition to eye, ear, facial, and occiput features, one may note the excessive skin on the back of the neck, the hypotonia and consequent hyperflexibility, decreased Moro, and dysplastic pelvis. Observation of hands may be useful, revealing shortened middle phalanges and associated incurving of the fifth digits, transverse palmar crease, and high incidence of arch and ulnar loop fingerprint features.

Birth incidence of mongols has been reported from one in 520 to one in 873. However, because of decreased life expectancy the population incidence has been reported from one in 2200 to one in 10,000. Random birth risk ranges from one in 1500 for mothers age 15-29 to one in 50 for mothers over forty-five.

However, if a mother under 30 years of age has a mongol child, the chance that this child has inherited a translocation of No. 21 is one in 50 or 2.0 percent. In other words, there is a relatively high chance that a young mother of a mongol child has herself a 21 chromosome joined to either a D-group or another G-group chromosome. She, however, has only one more No. 21 chromosome; her child has two 21 chromosomes, the normal number, but also a translocation 21 as well. The frequency of translocation among mongols is only 3.5 percent. The majority (96.5 percent) are

trisomy 21. If either parent is a translocation carrier, there is a theoretical 33 percent probability of having a mongol offspring — that is, the translocation-bearing parent can produce four types of gametes. One type contains a normal 21 chromosome, a second contains a translocated 21 chromosome, a third contains a normal 21 and a translocated 21, and a fourth contains no 21 at all. The third type gamete will, when joined to a normal gamete, result in a mongol. The fourth type gamete will result in a nonviable fetus and abortion will occur. Thus, the theoretical probability for such a parent having a mongol offspring is one in three since only three out of four gametic types result in a viable fetus. The actual birth incidence of mongols is only 10-20 percent if the mother carries the translocation, and only 2.0 percent if the father is the carrier. This suggests that there is a selection process, especially among males, for gametes resulting in phenotypically normal offspring. There is one small but important exception, however, — if either parent is a 21/21 translocation carrier rather than D/21 or 22/21 carrier, then the probability of that couple having a mongol child is 100 percent. This is because such a parent has only two types of gametes. One type inevitably has two 21 chromosomes and will result ultimately in a mongol. The other type has no 21 chromosomes and union will result in a nonviable fetus. Therefore, all liveborn children from that parent must be mongoloid. With the innovation of fluorometric chromosome analysis using quinicrine mustard, distinction between 21/21 and 22/21 translocation is now possible. Since the statistics are so greatly different, the distinction is well worth making for the sake of genetic counselling.

The most commonly associated malformation with Down's syndrome is congenital heart disease, usually involving endocardial cushion defects such as ventricular septal defect (VSD), atrial

septal defect (ASD), atrioventricular communis, or combinations of these defects. Patent ductus arteriosus (PDA) is also fairly common. Next in incidence are gastrointestinal malformations such as imperforate anus, congenital megacolon, and, in particular, those of the duodenum such as stenosis or atresia. Clubfoot and cataract are also found with a moderate frequency. Leukemia among mongols occurs three to 18 times more frequently than in the general population. It is usually acute or subacute, with mononuclear rather than granulocytic series predominance, and has a peak incidence from ages two to five years. Although speculation has arisen that this increased incidence may have some correlation with the Philadelphia chromosome, a G-group chromosome with partial deletion of its long arm, occurring in many cases of chronic myelogenous leukemia, it has now been shown by use of quinicrine mustard that the Philadelphia chromosome is a partially deleted 22 rather than 21 chromosome, and so there is no direct correlation with Down's syndrome.

Mongols constituted one-sixth of children with intelligence quotients (IQ) below 70 and one-third of children with an IQ below 54 in one study. Their average IQ seems to be about 35-40, with standard deviation about 10. The social quotient of young mongols is about three years ahead of IQ. But both social and intelligence quotient seem to drop with age, which suggests a tendency to an early developmental plateau. Attempts at medical management to improve IQ have been unsuccessful. The blood serotonin levels in trisomic (but not translocation) mongols were low. This suggested a trial of a serotonin precursor, 5-OH-tryptophan. However, the only effect was reversal of hypotonia in infant mongols, without beneficial effect on IQ. At present the most effective way of helping families who are predisposed to having phenotypically normal children seems to be *in utero* cytogenetic diagnosis, with

therapeutic abortion of mongol fetuses. Valenti and colleagues have reported a case in which a mother known to be a D/G translocation carrier was shown at three months gestation to be carrying a mongol. The fetus was aborted. When she becomes pregnant again, in utero cytogenetic diagnosis will again be performed. If the fetus is not mongoloid, she will carry it to term. This procedure seems benign enough to warrant its use with pregnant mothers at high risk of having a mongol offspring, e.g. mothers with translocations and perhaps even all mothers over forty-five.

PATAU'S SYNDROME (Trisomy 13)

In 1960 a syndrome associated with trisomy in the D-group (chromosomes Nos. 13, 14, 15) was reported. Tritiated thymidine analysis has indicated that the actual chromosome is No. 13. Incidence is estimated at one in 4600 to one in 14,500. The clinical picture is one of severe malformations centering about the facial structures and central nervous system (CNS). Facially the patients show microcephaly, large broad nose, hypotelorism, low-set ears, small eyes, small jaw, and cleft lip and palate. CNS malformation such as arrhinencephaly, cerebellar hypoplasia and agenesis of corpus callosum and olfactory lobes are manifested by seizures, mental retardation and apneic spells. Other anomalies easily found on examination include simian line, polydactyly, syndactyly, rocker-bottom feet, fifth finger overlapping fourth, hyperconvex nails, and capillary hemangiomas. There is involvement of multiple systems. Necropsy studies have shown cardiac malformations such as defects of septae, valves, and great vessels, and urogenital anomalies such as hydronephrosis, polycystic renal cortex, and bicornuate uterus. Interesting hematologic anomalies include persistence of fetal hemoglobin

(hemoglobin F) as well as persistence of an embryonic hemoglobin consisting of two alpha and two epsilon chains (Gower II). Polymorphonuclear leukocytes show pedunculated nuclear projections with hooklike appearance. Statistically, 70 to 80 percent of patients die within six months after birth.

EDWARD'S SYNDROME (Trisomy 18)

The frequency of this syndrome has been estimated to be from one in 4500 to one in 6500. It was initially described in 1960 as being the result of an extra chromosome within the E group (Nos. 16, 17, 18). In 1962 No. 18 was identified as the additional chromosome. Suspicion of the syndrome may arise simply from obstetric history. There is an association with polyhydramnios and small placenta. The affected offspring tend to be female and weigh less than six pounds. Neonatal examination may show a single umbilical artery, low-set and malformed ears, small jaw, overlapping of second over third fingers (also toes), six or more "arch" fingerprint patterns, prominent occiput, small pelvis with limited hip abduction, and muscular hypertonicity. Less commonly found characteristics include cleft lip or palate, simian crease, hypoplastic fingernails, and rocker-bottom feet. This disorder also affects many systems. Congenital heart disease, especially VSD, PDA, patent foramen ovale, and pulmonic stenosis are common. ASD and coarctation of the aorta are less frequently found. Multiple anomalies of central nervous, ophthalmic, urogenital, gastrointestinal, and other systems have been reported. As the child becomes older, mental defect and failure to thrive become more important. Ninety percent of affected children die within the first year. However, two such children, ages four

and nine, are at Sonoma State Hospital.

CRI DU CHAT SYNDROME

This syndrome is associated with a partial deletion of the short arm of a No. 5 chromosome. The name "cri du chat" refers to the feeble high-pitched cry, similar to a kitten's, which these children have from birth through about five months of age. The cry is associated with a small epiglottis and larynx. It has been postulated that the reason for disappearance of the cry is hardening of cartilage of epiglottis and larynx. The incidence of the syndrome is not known. It may be missed fairly often since clinical findings are not as characteristic as those of the trisomy syndrome and the peculiar cry may not be recognized as specific in a child with microcephaly and severe mental retardation. Patients also have moon face, hypertelorism, epicanthal folds, strabismus, low-set ears, and congenital heart disease. The fatality rate is comparatively low, but the majority of children require institutionalism because of the degree of their mental retardation.

CONCLUSION

Trisomies of autosomes other than 21, 13, or 18 comprise a minute portion of chromosome studies published to date. Trisomies for chromosomes Nos. one through twelve seem lethal early in embryonic life, because these trisomies have been found in spontaneously aborted fetuses, but not in living infants. Fifteen to twenty percent of pregnancies terminate as spontaneous abortions. Of these

about 30 percent in the first trimester and ten percent in the second trimester are associated with chromosomal abnormality. Thus, about five percent of conceptuses have demonstrable chromosomal abnormality. Perhaps fortunately, the majority are aborted.

Among other reported partial deletion syndromes are long arm of 18, short arm of 18, and short arm of four. The latter has been termed Wolf-Hirschhorn syndrome and has some similarities to cri du chat. However, it differs in having hypospadias, preauricular sinus, and absence of a catlike cry. Another type of abnormality is the ring chromosome. This may be formed when two broken ends of a chromosome reunite, leaving fragments of genetic material which usually disappear. The size of the deletion thus produced is variable. Any chromosome in the human complement may be replaced by a ring chromosome, and the phenotype associated with the resultant deletion may resemble that found in other syndromes, e.g. cri du chat. Most of the autosomal ring chromosomes reported in man have occurred in the D and E-groups.

The question arises as to when to do a chromosomal analysis. In most instances analyses are normal in patients with only odd facies or mental retardation or growth failure or single major malformation such as congenital heart disease. Study is not indicated in a patient with a multiple malformation syndrome known to be caused by a mutant gene, such as Ellis-van Creveld syndrome. But for the patient with multiple malformations which do not fit a known pattern, chromosome studies are indicated. However, no clinical presumption of a chromosomal abnormality can be made in such a patient. For example, in one study of 50 such children, only four were found to have chromosomal abnormality.

*SUGGESTED READING**

Caspersson T, Zech L, Johannsson C, et al: Identification of human chromosomes by DNA-binding fluorescent agents. Chromosoma (Berlin) 30:215-227, 1970

Gellis SS, Feingold M: Atlas of Mental Retardation Syndromes. Washington, D.C.: United States Government Printing Office, 1968

Nelson WE (ed): Textbook of Pediatrics, 9th edition. Philadelphia: W.B. Saunders Company, 1969

Penrose LS, Smith GF: Down's Anomaly. Boston: Little, Brown and Co., 1966

Schulz J: Chromosome disorders in mental retardation. Pediat Clin N Amer 15:817-888, 1968

Tjio JH, Levan A: The chromosome number of man. Hereditas 42:1-6, 1956

Valenti C, Schutta EJ, Kehety T: Cytogenetic diagnosis of Down's syndrome in utero. JAMA 207:1513-1515, 1969

*A more inclusive bibliography may be obtained from author.

Ability, *n.* The natural equipment to accomplish some small part of the meaner ambitions distinguishing able men from dead ones. In the last analysis ability is commonly found to consist mainly in a high degree of solemnity. Perhaps, however, this impressive quality is rightly appraised; it is no easy task to be solemn.

AMBROSE BIERCE, *circa 1860*
The Devil's Dictionary
(New York: Dover 1958)

CEREBRAL BLOOD FLOW

MAJ Michael Bronshvag, MC*

It has been 25 years since basic principles for studying cerebral blood flow were outlined. /1-3/ Several modifications and improvements have appeared. Both total /4/ and regional /5/ flow can be measured now, and the regional flow can be roughly divided into gray matter flow, white matter flow and shunt flow /6/. These techniques have been used by laboratory researchers and clinicians to measure cerebral blood flow (CBF) and changes in CBF in experimental and clinical settings. A veritable mass of data, facts, and speculations have appeared; however, it is seldom that an individual patient is directly benefitted by having such studies performed.

Measurement of total and regional CBF can be performed in several ways. Each method capitalizes on some anatomic or physiologic characteristic of the brain and head of the species with which one is working, and each is modified by the needs of the clinical or experimental setting.

One can simply measure large vessel flow to or from the head (e.g.,internal or common carotid artery, jugular vein) using an electromagnetic-sensing flow probe (Doppler effect). /7/ In humans, each internal carotid artery supplies mainly cerebral tissue and is responsible for 40 percent of total CBF. In experimental animals, most of whom do not possess as large a brain as man, the internal carotid may be the terminal branch of a carotid system which mainly supplies the face and hence it is not suitable to use in investigations. The internal jugular veins in humans drain most of the cerebral blood. They are easy to puncture. In lower animals, they are small, multiple, inconstant, and are not well-suited for most experimental designs.

Most techniques are related to capillary bed transit time and are dependent on capillary-tissue exchange of a marker

*Formerly Resident, Neurology, Letterman General Hospital, and presently assigned to Letterman Army Institute of Research.

substance, i.e. they are modifications of the well-known Fick principle. The direct Fick principle depends upon sampling an artery and its homologous vein and deriving total flow from changes in concentration of the marker substance. It assumes that the arterial and venous concentrations vary only with time and not with sampling location. The direct Fick principle is not well-suited for studying cerebral blood flow, because the arterial and venous channels are dissimilar (indeed each artery, vein and sinus is relatively unique).

In a derivation of great importance and elegance, Kety and Schmidt /1-3/ modified the Fick principle by measuring rate of uptake of an inhaled gas (N_2O) from zero concentration to equilibrium (saturation technique, also called Kety-Schmidt technique). Since the concentration of N_2O should be roughly equal in every arteriole in the body, the arteriovenous difference reflects flow per weight of tissue. A simplication of the original procedure is the desaturation technique. Assuming normal pulmonary function, the arterial concentration will be zero during desaturation and therefore blood flow per unit weight of tissue is simply related to rate of change of venous concentration. Also, since during desaturation of and inhaled inert gas arterial concentration is zero, blood flow per unit weight of tissue is related directly to change in parenchymal concentration of the marker substance. Brain parenchymal weight can usually be accurately estimated.

Thus cerebral blood flow can be measured using an inert inhaled gas (N_2O /1-3/, H_2 /8/, Kr /4/, Xe /9/, et cetera) and measuring either venous effluent (jugular bulb puncture /3,4/, sagittal sinus cannulation) or estimation of tissue concentration (external counting of a radionuclide — ^{133}Xe, ^{79}Kr /10/, direct microelectrode tissue measurement /11,12/). The venous techniques give relatively total CBF figures, while the parenchymal techniques using external scintillation counters or direct puncture regional microelectrode technique obviously give regional CBF figures.

Since the calculation of CBF depends upon analysis of a curve, that curve can be simply treated as a single variable ("stochastic" technique) or subjected to further scutiny (compartmental analysis /6/). Using the latter technique, it was noted that most CBF curves could be soundly split into four compartment curves, very fast, fast, slow, and very slow, with regard to speed of saturation or desaturation. These roughly correspond to shunt flow (very fast), gray matter flow (fast),

white matter flow (slow) and nonparenchymal tissue flow — e.g. bone, ligaments, (very slow).

A final modification of the desaturation technique involves saturation via bolus injection into the carotid system (often during an arteriogram /10/). As mentioned already, this technique is best suited for humans who have large internal carotid arteries, and is less suited to the needs of the experimenter using animals.

These techniques have been used to study normals and patients suffering from many diseases related to, or reputedly related to abnormalities in CBF, and to study the response of normals, ill patients and laboratory animals to changes in environment (O_2, CO_2, blood pressure, various drugs, et cetera). /13,14/

It was quickly confirmed that hypoxia, hypercarbia and acidosis increased CBF and that most drugs had but little effect. These findings are compatible with the current thoughts on cerebral autoregulation. /13, 14/ Furthermore, it was shown that most changes in CBF are changes in fast-gray matter flow, which correlates with pial-cortical-arteriolar flow. In "cerebral death", flow drops, but more importantly oxygen consumption drops markedly, and the cerebral corter behaves much like a shunted tissue. /15/

It has been shown that total cortical blood flow decreases in senile and presenile dementias, and that most of this loss is in fast-gray matter flow. /16/ To the despair of the drug companies, blood flow per weight of remaining gray matter is roughly normal. These studies seem to suggest that many dementing illnesses are not due to primary alterations in CBF and that vasodilating drugs might not be expected to be helpful. Patients suffering from transient ischemic attacks usually have normal regional cerebral blood flow to the affected area of their brain, and by inhaling carbon dioxide, they can further increase local flow to these areas. This suggests that transient ischemic episodes are not usually secondary to areas of marginal blood flow and lends indirect but important support to the now widely accepted theory that most transient ischemic attacks are caused by emboli. /17/ Patients with acute thromboembolic strokes who have angiographically demonstrable occlusions tend to have decreased regional CBF /18, 19/ and those who have no demonstrable occlusion may have decreased, normal, or increased regional CBF /20/ (reactive hyperemia, "luxury perfusion" /21/). Administration of vasodilating agents to patients with demonstrable occlusions is likely to cause vasodilation

primarily in unaffected areas and further decrease flow to the affected area (intracerebral steal). /18, 20/ Therefore many clinicians feel that vasodilating drugs do not have a place in the management of the stroke syndrome.*

Worthy of passing mention are the methods of measuring CBF designed only for experimental animals, such as the use of microspheres emboli to the brain followed by examination of cut brain section. Also noteworthy are clinical radionuclide "flow studies" (measuring perfusion and not flow) which are semi-quantitative and best-suited for determining whether large vessels are patent or not, and a rough estimation of CBF by evaluation of angiographic circulation time.

Studies of CBF have revealed or confirmed many important principles but none of them are compelling reasons for studying CBF in an individual patient. Studies of regional CBF using inhalation techniques rather than carotid puncture are safe and may give interesting data, but at present they do not seem to suggest new therapies for the stroke patient. Most patients with transient ischemic attacks or repeated minor strokes probably are having repeated emboli rather than a primary disease of CBF. /17/ An occasional patient with arteriosclerosis or slowly progressive vasculitis will have symptoms related to inadequacy of CBF and may be studied by regional desaturation CBF measuring technique, but can usually be adequately managed without these studies.

The CBF studies may have a role in screening asymptomatic middle-aged populations for vascular disease, and will continue to have an important role in the study of disease processes in clinic and experimental laboratory, but only a minor role in handling of the next challenging case.

*We do not recommend angiography for the patient with an acute stroke.

References

1. Kety SS, Schmidt CF: The determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. Amer J Physiol 143:53-66, 1945
2. Kety SS, Schmidt CF: The effects of active and passive hyperventilation on cerebral blood flow, cerebral oxygen consumption, cardiac output and blood pressure of normal young men. J Clin Invest 25:107- 1946
3. Kety SS, Schmidt CF: Nitrous oxide method for quantitative determination of cerebral blood flow in man: theory, procedure, and normal values. J Clin Invest 27:476-483, 1948
4. McHenry LC: Quantitative cerebral blood flow determination: Application of krypton 85 desaturation technique in man. Neurology 14:785-791, 1964
5. Lassen NA, Høedt-Rasmussen K, Sørensen SC et al: Regional blood flow in man determined by krypton^{85}. Neurology 13:719-727, 1963
6. Obrist WD, Thompson HK Jr, King CH, et al: Determination of regional cerebral blood flow by inhalation. Circ Res 20:124-135, 1967
7. Kristiansen K, Krog J: Electromagnetic studies on the blood flow through the carotid system in man. Neurology 12:20-22, 1962
8. Gotoh F, Meyer JS, Tomita M Hydrogen method for determining cerebral blood flow in man. Arch Neurol 15:549-559, 1966
9. Isbister WH, Schofield PF, Torrance HB: Cerebral blood flow estimated by ^{133}Xe clearance technique. Arch Neurol 14:512-521, 1966
10. Høedt-Rasmussen K: Regional cerebral blood flow. The intra-arterial injection method. Acta Neurol Scand 43 (suppl 27) 1967 79pp
11. McHenry LC Jr, Jaffe ME, Goldberg HI: Regional cerebral blood flow measurement with small probes. I. Evaluation of the method. Neurology 19:1198-1206, 1969
12. Jaffe ME, McHenry LC Jr, Goldberg HI: Regional cerebral blood flow measurement with small probes. II. Application of the method. Neurology 20:225-237, 1970
13. Lassen NA: Cerebral blood flow and oxygen consumption. Physiol Rev 39:183- 1959
14. Meyer JS, Gotoh F, Tazaki Y, et al: Regional cerebral blood flow and metabolism in vivo. Effects of anoxia, hypoglycemia, acidosis. alkalosis, and alterations of blood PCO_2. Arch Neurol 7:360-581, 1962

15. Shalit MN, Beller AJ, Feinsod M, et al: The blood flow and oxygen consumption of the dying brain. Neurology 20:740-748, 1970
16. Obrist WD, Chivian E, Cronqvist S, etal: Regional cerebral blood flow in senile and presenile dementia. Neurology 20:315-322, 1970
17. Skinhøj E, Høedt-Rasmussen K, Paulson OB, et al: Regional cerebral blood flow and its autoregulation in patients with transient focal cerebral ischemic attacks. Neurology 20:485-493, 1970
18. Paulson OB: Regional cerebral blood flow in apoplexy due to occlusion of the middle cerebral artery. Neurology 20:63-77, 1970
19. McHenry LC: Cerebral blood flow studies in middle cerebral artery occlusion and in internal carotid artery occlusion. Neurology 16.1145-1151, 1966
20. Paulson OB, Lassen NA, Skinhøj E: Regional cerebral blood flow in apoplexy without arterial occlusion. Neurology 20:125-138, 1970
21. Høedt-Rasmussen K, Skinhøj E, Paulson OB, et al: Regional cerebral blood flow in acute apoplexy. The "luxury perfusion syndrome" of brain tissue. Arch Neurol 17:271-281, 1967

THE MANAGEMENT OF CEREBRAL EDEMA WITH ORAL GLYCEROL

MAJ Tracy A. Newkirk, MC

The problem of cerebral edema presenting in patients with a variety of diseases always challenges the physician's management skills. Not only can brain edema be life-threatening or introduce serious morbidity, but the classical methods of treatment have also involved numerous complications. Glucose, mannitol, and urea are all capable of reducing intracranial pressure transiently. Glucose crosses the blood-brain barrier and is rapidly metabolized providing only a few minutes of osmotic dehydration of the brain. Mannitol and urea provide longer periods of dehydration but still too short for clinical usefulness except in diagnostic trials relating symptoms to brain edema and preoperative shrinkage of the edematous brain. Both have the serious problem of being taken up by lesions in which the blood-brain barrier has been altered. Since they are not metabolized they then exert their osmotic effect toward greater accumulation of fluid in the lesion contributing to increase of the mass effect and intracranial hypertension. Even with an intact blood-brain barrier, urea eventually crosses into cerebral tissue in sufficient quantities to reverse the osmotic gradient. Urea has also been implicated in the extension of subarachnoid hemorrhage. Both agents induce a significant diuresis and accompanying this is a strong potential for electrolyte imbalance.

Glucocorticoids and ACTH have been shown to reduce intracranial pressure effectively. Reduction of pressure does not occur until approximately twelve hours following the first dose and full reduction usually requires

twenty-four hours. Well-known side reactions attend the use of steroids. These include gastrointestinal irritation, psychic reactions, and alterations of the host's immune responses. Additional problems are encountered during long-term therapy. The ideal agent for reduction of intracranial pressure should be capable of rapid and sustained reduction of cerebral edema without rebound rehydration and with freedom from other adverse side-effects.

Glycerol, a naturally-occurring 3-carbon trihydric alcohol, is a highly effective osmotic agent capable of accomplishing cerebral dehydration without causing massive diuresis. Virno et al /1,2/ established the potential usefulness of this agent by controlling experimental cerebral edema in rabbits. Later Cantore et al /3,4/ reported a large series of patients with cerebral edema without rebound rehydration. There was no toxicity in these patients with the exception of nausea and vomiting. No electrolyte disturbances occurred and diuresis was not a problem. Many additional reports have appeared documenting the safety and efficacy of oral glycerol as an anti-edema agent and the use of this drug has become routine in many neurologic practices. Glycerol has also been used for the reduction of intraocular pressure. It is well-established practice to use glycerol as a preservative in storing whole blood. Concentrations as high as 52 percent have been employed. Hemolysis of stored cells, which has occurred on occasion, has been attributed to the freezing and thawing techniques rather than to the glycerol.

There is a general impression prevalent among clinicians that glycerol causes hemolysis, hemoglobinuria, and albuminuria. This idea stems primarily from work done with animals in which glycerol was given intravenously, intraperitoneally, or subcutaneously. It was learned that the subcutaneous and intraperitonal routes uniformly produces hemolysis. Glycerol in

solution with water in concentrations greater than 20 percent also caused the same unwanted effects on red blood cells. No difficulties were encountered with glycerol in saline in concentrations of ten percent or less. There are no reports of hemotoxicity from oral glycerol in long-term studies in animals or man. High doses have been given to patient volunteers for as long as fifty consecutive days (1.3 - 2.2 gm/kg/day) and for as long as fifty weeks in dogs whose diets have included 35 percent undiluted glycerol by volume. /5/

It is difficult to find any reports of adverse effects from oral glycerol in humans beyond the frequent occurrence of nausea and vomiting. Headache and dizziness have been mentioned. /6,7/ D'Alena et al /7/ reported an 82-year-old woman with hypertension who was given a single oral dose of 2.0 gm/kg. Several hours later she developed headache, nausea and shaking in one arm. Glycerol was stopped and the patient became asymptomatic over a period of several days. A second patient with diabetes mellitus developed moderately severe diabetic acidosis two days after initiation of glycerol. After stopping the glycerol and regulating his insulin dosage, control was again established. It was thought unlikely that glycerol contributed directly to the problem.

Glycerol has been given parenterally to humans. The first recorded case was by Bowesman. /8/ He injected 2-3 ml of ten percent glycerol repeatedly into the femoral artery for control of edema due to filariasis. Good reduction of leg circumference without side-effects was accomplished over forty days. Sloviter /9/ studied the effects of glycerol remaining in preparations of washed erythrocytes. He gave five percent glycerol in saline intravenously up to 1.2 gm/kg/day with no ill-effects. Electrocardiographic monitoring and serial determinations of plasma hemoglobin

revealed no abnormalities. Cantore et al /4/ infused 30 percent glycerol in ten percent dextrose in a dose of 0.8 - 1.0 gm/kg and achieved marked reduction in intracranial pressure. This route received only limited application allegedly because of transient hemoglobinuria. No documentation of side-effects was given. Wolf et al /10/ gave glycerol intravenously to newborn infants without ill-effects. Four-week-old infants had elimination rates nearly as high as adults.

Other reports of intravenous glycerol in humans generally discuss thirty percent solutions given for reduction of intraocular pressure. When given in combination with sodium ascorbate (0.6 gm/kg glycerol and 0.28 gm/kg sodium ascorbate) no hemolysis or hemoglobinuria was noted.

Turnover and Excretion

Free glycerol can be found in human plasma and the concentration can be increased by norepinephrine or decreased by insulin. During starvation and in hyperthyroidism plasma glycerol concentrations may rise as high as 3-4 mg/100 cc. Glycerol has been given to diabetic patients during partial insulin withdrawal and this has resulted in a decrease in ketones and in glycosuria, suggesting that glycerol may be metabolized without the aid of insulin.

The liver removes 80-90 percent of circulating glycerol and the kidney the remainder. This distribution fits available data for the distribution of glycerokinase. /11/ Glycerol distributes throughout the extracellular space and it appears to equilibrate with tissue water within minutes if given by continuous intravenous infusion. At plasma concentrations of glycerol of 1.0 mg/100 cc or less, urine glycerol concentration approaches zero. With increasing

plasma levels, glycerol appears in the urine in increasing amounts. It is assumed that tubular lumen cells are able to convert small quantities glycerol to CO_2, glucose and lactate. Only at the point that their glycerokinase becomes saturated does glycerol escape into the urine.

The advantage conferred by the renal threshold for excretion of glycerol is protection against unwanted diuresis. Mannitol and urea on the other hand are not reabsorbed in the tubular lumen leading to renal excretion of a major portion of the administered dose along with large volumes of fluid. Attendant on this diuresis is a high potential for electrolyte imbalance and dehydration.

Glycerol penetrates all tissues readily with the exception of the brain. Since glycerol reduces intracranial pressure in nephrectomized animals, renal excretion of fluid is not needed as part of the mechanism of brain dehydration. Fluid removed from brain is retained in the intravascular space and to some extent is redistributed to other tissues. Overloading the intravascular compartment leading to peripheral edema and congestive heart failure does not occur. If data from animal work can be extrapolated to humans, only 100 ml of fluid need be removed from the brain to achieve marked reduction in intracranial pressure. /12-14/ The addition of such small volumes of fluid to the intravascular compartment should cause no cardiac overload. If fluid overload were a problem, the part contributed by glycerol could almost certainly be overcome with fluid restriction and diuretic therapy.

There is some evidence that the rebound overshoot in intracranial pressure following administration of urea is related to slow entry of urea into brain tissue thereby creating a reverse osmotic gradient and an accompanying movement of water into the brain. It is not clear whether or not this mechanism applies to

mannitol. Studies utilizing radioactive glycerol in simultaneous perfusions of the intraventricular and intravascular spaces indicates that there is a highly effective barrier to the passage of glycerol, totally excluding it from the normal brain. Other studies with labelled glycerol indicate that it disappears from the blood no more rapidly than Evans' blue dye which is also thought not to pass the blood-brain barrier.

There is evidence, although not fully conclusive, that glycerol is metabolized by the brain. If this is true, glycerol crossing the blood-brain barrier at sites of interruption by a pathologic process would be metabolized, analogous to glucose, thereby circumventing the danger of developing a reverse osmotic gradient.

Glycerol has a nutrient value of 4.32 cal/gm which is a greater caloric yield than an equal amount of glucose. Glycerol can therefore make a nutritional contribution to the patient with increased intracranial pressure. This is often an important consideration, because such patients are commonly unable to sustain adequate nutrition without assistance.

Recommendations for the Clinical Use of Glycerol

When the diagnosis of intracranial hypertension has been established and appropriate therapeutic measures considered, glycerol may be employed for either short- or long-term reduction of pressure. Currently, only the oral route has approval for clinical use and more work is needed to set guidelines for intravenous administration. Glycerol may be given orally both to inpatients and outpatients and even to patients with a compromised level of consciousness, provided sufficient precautions are observed.

Treatment should always be initiated on an inpatient basis in order to document the patient's response and to determine the exact dose needed. Generally 0.5 to 1.0 gm/kg body weight will suffice, if given every 4-6 hours. Patients with mild enough involvement to permit outpatient management may require less. Since pure glycerol is intolerably sweet, it must be diluted in lemon, orange, or tomato juice. Most patients receiving low doses can tolerate diluted glycerol. For those who have difficulty with nausea, it is advisable to administer an antiemetic thirty to sixty minutes before each dose. During the first few days of therapy, the physician can document the response to glycerol by doing a lumbar puncture before a given dose and checking the pressure at intervals in order to establish a dose-response relationship upon which to pattern continuing therapy. When the dose pattern has been determined, cerebrospinal fluid pressure should be rechecked at whatever intervals are appropriate for a given patient's clinical condition. When CSF pressure has stabilized within normal limits, glycerol therapy may be stopped suddenly without ill-effect.

Patients who are seriously ill may be given glycerol by nasogastric tube in a pattern similar to that described above. Additional precautions against vomiting may be taken because of the increased danger of aspiration in obtunded patients. Glycerol in the same doses may be mixed with the patient's nasogastric feedings. He should be placed with the head elevated 30 degrees for half an hour after each dose. Routine premedication with parenteral antiemetics should be used whenever needed. The response of the CSF pressure should also be documented with lumbar punctures. If the patient is not receiving nasogastric feedings, it is advisable to mix the glycerol with juice.

CASE REPORTS

CASE 1. A 15-year-old obese boy was seen in the emergency room with a complaint of fever and ear pain. Examination revealed a left otitis media. No other abnormal findings either on examination or laboratory study were present. He was treated with antibiotics with resolution of fever and pain. Two days later he returned with diplopia, nausea, vomiting and headache. The symptoms were transient and no abnormalities could be found on examination. One week later the symptoms became persistent and bilateral sixth nerve palsies were noted. The patient was admitted to the hospital for study. Skull series, brain scan and bilateral carotid arteriography were normal. CSF pressure was 370 mm H_2O with a normal protein and no cells. Cultures were negative. The patient was treated with glycerol by nasogastric tube, 1.0 gm/kg with prompt clearing of his symptoms. Fifteen days later, the glycerol was discontinued without recurrence of symptoms. Spinal fluid pressure twenty-four hours after stopping glycerol was 160 mm H_2O. Diagnostic considerations in this boy included brain abscess, lateral sinus thrombosis, and pseudotumor cerebri. Since examinations and special studies were normal except for nonspecific signs of intracranial hypertension, the last possibility was thought to be the most feasible.

CASE 2. A 19-year-old male college student who was otherwise in good health began to demonstrate episodes of bizarre and antisocial behavior. Over a period of one week he became progressively

withdrawn and more bizarre in his behavior. He was admitted to a psychiatric service for diagnosis and treatment. During a week there he entered a state resembling catatonic schizophrenia. Shortly thereafter he spiked a fever to 104 F. No etiology for the fever could be found until a lumbar puncture revealed fifty monocytes with a normal protein, and negative cultures. CSF pressure was 200 mm H_2O. A diagnosis of encephalitis was made. The patient was transferred to the neurology service for treatment. Eventually Echo III virus was grown from the spinal fluid. During the first week of treatment he developed focal seizures manifested by turning of the head and eyes to the left and occasionally with jerking movements of the left hand and arm. These never became generalized. He developed gastrointestinal bleeding which responsed well to conservative measures. When he failed to show any improvement after one week, a repeat lumbar puncture was done. Again there were fifty monocytes with a normal protein and sugar but the pressure was 500 mm H_2O. Glycerol, 1.0 gm/kg was administered via nasogastric tube every six hours. The CSF pressure began to drop sharply seventeen minutes after giving the dose and remained within normal range for approximately five hours. TABLE I. The patient's level of consciousness improved within twelve hours after the initial dose of glycerol. With this improvement the dose of glycerol was reduced by half because of his vomiting. Reduction of spinal fluid pressure was equally effective with the lower dose. The patient continued to receive glycerol for three weeks, after which it could be discontinued with the pressure remaining within normal limits.

TABLE I

RESPONSE OF CEREBROSPINAL FLUID PRESSURE TO ORAL GLYCEROL*

DATE	CEREBROSPINAL PRESSURE (mm H_2O)	INTERVAL AFTER DOSE	COMMENT
8 September	500	At time of initial dose	Dose = 1.0 gm/kg glycerol
8 September	320	17 min after first dose	every six hours
8 September	240	15 min after second dose given 6 hours after initial dose	
9 September	140	3 hours after dose	Dose reduced to 0.5 gm/kg because of vomiting†
14 September	410	6 hours after dose	Demonstrates need for continuing therapy
21 September	130	4 hours after dose	
28 September	140	24 hours after dose	
29 September	Stabilized within normal limits		Glycerol therapy discontinued

*Case 2. Therapy was administered via nasogastric tube.

†The reduction of spinal fluid pressure was equally effective with the lower dose. It was suggested that perhaps this was related to some resolution of the CNS inflammatory process.

The patient's convalescence lasted about five months. Six months following his discharge from the hospital, neurologic and psychologic testing revealed no abnormalities. He had resumed his studies a few weeks before his return visit and appeared to be having no difficulty with them.

COMMENT

The collective experience of many investigators using oral glycerol as an osmotic anti-cerebral edema agent confirms its safety and effectiveness. With rare exceptions, the only sign of toxicity is gastrointestinal irritation. The disturbances of fluid and electrolyte balance and rebound rehydration of the brain seen with urea and mannitol do not occur with glycerol. The multitude of potential problems associated with corticosteroid therapy have not been found to result from glycerol administration.

There is already information that glycerol can be safely administered intravenously but further data must be accumulated before intravenous glycerol is used clinically. The Neurology Service at Letterman General Hospital is conducting research on the question of using intravenous glycerol and we are attempting to demonstrate its usefulness and safety before introducing it as a therapeutic agent.

It is hoped that glycerol will receive wider application as a cerebral dehydration agent because of its high degree of effectiveness, safety, relative freedom from unwanted side reactions, and ease of administration.

References

1. Virno M, Chiavarelli A, Cantore GP: Azione del glicerolo sulla edema cerebrale nel coniglio dopo craniectomia. Gazz Int Med Chir 66:3509-3515, 1961
2. Virno M, Cantore GP, Bietti C, et al: Azione del glicerolo sulla pressione endoculare dei conigli. Boll Oculist 41:815-821, 1962
3. Cantore GP, Guidetti B, Virno M: Oral glycerol for the reduction of intracranial pressure. Exerpta Medica International Congress. Series 60:128, 1966
4. Cantore GP, Guidett B, Virno M: Oral glycerol for the reduction of intracranial pressure. J. Neurosurg. 21:278-283, 1965
5. Johnson V, Carlson AJ, Johnson A: Studies on the physiological action of glycerol on the animal organism. Amer J. Physiol. 103:517-534, 1933
6. Buckell M, Walsh L: Effect of glycerol by mouth on raised intracranial pressure in man. Lancet 2:1151-1152, 1964
7. D'Alena P, Ferguson W: Adverse effects after glycerol orally and mannitol parenterally. Arch Ophthal 75:201-203, 1966
8. Bowesman C: Intra-arterial glycerin treatment of elephantiasis. Brit J Surg 26:86-89, 1938
9. Sloviter HA: Effects of intravenous administration of glycerol solutions to animals and man. J Clin Invest. 37:619-626, 1958
10. Wolf H, Melichar V, Michaelis R: Elimination of intravenously administered glycerol from the blood of newborns. Biol Neonat 12:162-169, 1968
11. Wieland O, Suyter M: Glycerokinase. Isolierung und Eigenschafter des Enzyms. Biochem Z 329:320-321, 1957

12. Shenkin HA, Bouzarth WF: Medical progress: Clinical methods of reducing intracranial pressure; role of the cerebral circulation. New Eng J Med. 282:1465-1471, 1970
13. Reed DJ, Woodbury DM: Effects of hypertonic urea on cerebrospinal fluid pressure and brain volume. J Physiol. 164:252-264, 1962
14. Reed DJ, Woodbury DM: Effect of urea and acetazolamide on brain volume and cerebrospinal fluid pressure. J Physiol 164:265-273, 1962

Potable, *n.* Suitable for drinking. Water is said to be potable; indeed, some declare it our natural beverage, although even they find it palatable only when suffering from the recurrent disorder known as thirst, for which it is a medicine. Upon nothing has so great and diligent ingenuity been brought to bear in all ages and in all countries, except the most uncivilized, as upon the invention of substitutes for water. To hold that this general aversion to that liquid has no basis in the preservative instinct of the race is to be unscientific—and without science we are as the snakes and toads.

AMBROSE BIERCE, *circa 1880*
The Devil's Dictionary
(New York: Dover 1958)

EVALUATION OF THE DIZZY PATIENTS

CPT Lynn Miller, MC

One of the most difficult problems the physician faces in his practice is the evaluation and management of the patient who describes himself as being "dizzy". The differential diagnosis of dizziness is staggering; the workup can be exhausting; and the management may be far from satisfactory for either the patient or the doctor. The purpose of this monograph is to outline an approach to the evaluation of the dizzy patient.

The first and basic problem facing the physician is to decide what the patient means when he states he is "dizzy". To resolve this, the doctor must seek the fuller description of the symptom by the patient and assign the appropriate term to it. The simplest solution is to place the description of the patient's symptom into categories of either vertigo or non-vertiginous dizziness.

Concisely defined, "vertigo is a hallucination of movement, either of the surroundings or of the patient himself." This concept should be broadened to include any sensation of movement, of himself or of his environment, as perceived by the patient. It is relatively unimportant in the evaluation of vertigo to determine whether the patient feels himself or his surroundings moving. Commonly associated with vertigo are symptoms of disturbance of other systems, i.e. vomiting, autonomic disturbances, vasomotor collapse, and sometimes loss of consciousness.

After establishing that what the patient describes is vertigo, it may be implied that disordered function exists in the vestibular system, anywhere from the labyrinths through the vestibular nucleii to their more central connections.

Non-vertiginous dizziness may now be defined as dizziness not associated with a hallucination of movement. This symptom has several causes, not referable to the vestibular system or its connections.

Anatomy and Physiology

Maintenance of normal relationships between the body and environment depends on afferent impulses from the eyes and labyrinths, plus proprioceptive input from eye muscles, neck, trunk and lower limbs. One of the most important of the peripheral structures in maintaining equilibrium is the labyrinth with its central connections — the vestibular system.

The labyrinth is the end-organ of the vestibular system. It is located in the petrous part of each temporal bone, and has both bony and membranous structures. The membranous portion is suspended in the similarly shaped bony part, separated from it by perilymph and consisting of three semicircular canals, a saccule and utricle (within a bony vestibule), and the cochlear duct (for hearing), all filled with endolymph and interconnected. The utricle and saccule are lined with a low epithelium containing a flat thickening, called a macula. The macula is composed of columnar cells and sensory cells over which lies a gelatinous layer containing crystals called otoliths. The peripheral fibers of the vestibular nerve are directed to the sensory cells. The semicircular canals are oriented in planes perpendicular to each other and each have both ends opening into the vestibule. At one end of each loop is a

dilitation called an ampulla, within which is a transverse ridge of tissue (the cristae). Each crista has sensory cells also projecting in to a gelatinous mass called the cupula. Also directed to each crista are peripheral elements of the vestibular nerve.

Vestibular nerve endings from the two maculae and the cristae unite and pass through the internal auditory canal. Together they pass with the auditory division of the eighth cranial nerve through the cerebellopontine angle to terminate in the upper medulla and lower pons. The primary vestibular nerve fibers terminate on the four vestibular nuclei of the ipsilateral side of the medulla and pons, except for some fibers which go directly to the cerebellum, to opposite vestibular nuclei, or to reticular formation.

Secondary vestibular fibers either ascend or descend in the brain stem. Descending fibers go to the anterior horn cells at all spinal cord levels , terminate on the anterior cells, which influence motor neurons. Ascending fibers go to motor nuclei of cranial nerves of both sides. They innervate eye muscles by way of the medial longitudinal fasciculus, as well as innervate or influence the vagus and glossopharyngeal nerves, and motor neurones to muscles of the neck. Other fibers ascend into the cerebellum, as well as the cerebral cortex of the contralateral side. The medial longitudinal fasciculus is a composite bundle of fibers in the brain stem and upper cervical spinal cord, mainly connecting vestibular nuclei, nuclei of cranial nerves of ocular motion and cranial nerves of cervical and facial movement. It thus constitutes a pathway for reflex control of head, neck, and eye movements in response to vestibular stimulation.

The labyrinth together with retinal and proprioceptive input assists in maintaining

equilibrium during active or passive movements of the body, or while at rest. The utricle and saccule record the position of the body in space as well as aiding postural adjustments through the distribution of muscle tone in response to changes of position of the head. The semicircular canals respond to rotational acceleration of the head in vertical, transverse or anteroposterior axes and aid in the coordination of eye movements with the head movements. Therefore, the maculae are receptors for perception of position related to gravity and the cristae are receptors for perception of movements.

CLINICAL EVALUATION

The evaluation of the dizzy patient is comprised of a general physical examination with special attention paid tothe cardiovascular system and thorough neurologic and ear, nose and throat examinations with special attention paid to the vestibular system.

To better understand the results of the clinical evaluation, it is helpful to be aware of the concept that labyrinthine influences on the brain stem are normally balanced by each other. An individual labyrinth's tonic influence on the brain stem (unopposed by the opposite labyrinth) would, in an awake patient, tend to cause nystagmus to the same side. To state it differently, a lesion which destroys or causes hypofunction of a labyrinth on one side, results in nystagmus toward the normal side.

It is important to first observe the patient's standing or walking with his eyes open and closed. With unilateral vestibular disease causing decrease in vestibular tonus, the patient tends to stagger or drift toward the involved side.

Observation for spontaneous vestibular nystagmus should always be made. Vestibular nystagmus is a rhythmic oscillation of the eyes with a fast movement in one direction and slow movement in the opposite direction. The direction of the fast component is considered by convention to be the direction of the nystagmus. The associated symptoms of past-pointing, falling and sensation of turning are toward the opposite side (side of decreased vestibular tone). Spontaneous vestibular nystagmus should be differentiated from other forms of nystagmus not usually associated with vertigo and not related to vestibular dysfunction. Pendular nystagmus is usually related to ocular defects and is characterized by oscillations of the orbits of equal speed in each direction in primary gaze and resembling central vestibular nystagmus in lateral gaze. Congenital nystagmus and latent nystagmus are similar in appearance. Optokinetic nystagmus is phasic like vestibular nystagmus but is a normal response evoked by looking at a series of figures moving across the field of vision.

Spontaneous vestibular nystagmus may be caused from peripheral or central vestibular lesions. Anatomically speaking, "peripheral" means from the labyrinth to the synapse of the primary neurons on the vestibular nucleus. "Central" means from the vestibular nuclei to their connections with the brain stem, spinal cord, cerebellum or cerebrum. Criteria to help differentiate central from peripheral nystagmus are presented in TABLE I.

Positional nystagmus, if present, is evoked by turning the patient's head toward one side and quickly lying him down backwards, facing first one direction and then the other. It may be of two types. Benign positional nystagmus, is typically rotary, directed towards the undermost ear, occurs after a brief latent period and may reverse directions

on sitting up. This is generally not reproducible on immediate successive repetitions. It is a sequela of head injury, infection, or vascular disturbance effecting the vestibular end-organ and is usually associated with severe vertigo. The central type of positional nystagmus more likely has a serious etiology, often suggesting posterior fossa masses, basilar-vertebral insufficiency, or demyelinating disease. Typically, when one tests for this type, it occurs immediately after assuming the test position and is accompanied by mild or absent subjective vertigo. The direction of the nystagmus may vary and the nystagmus is perpetual.

Caloric testing is an extremely valuable procedure in detecting labyrinthine disease and can be easily done with warm, cool or cold water in the office or on the ward. This test depends on the fact that when the tympanic membrane is warmed or cooled, the thermal change is transmitted to the semicircular canals and by convection currents the endolymph moves up or down (depending on the temperature of the water) in a vertically positioned semicircular canal. In the case of cold water, the movement is down in the lateral semicircular canal (the head is positioned 30 degrees up from the horizontal plane) and results in a decrease of vestibular tonic impulses. Nystagmus is produced in a normal awake individual to the side of the unstimulated labyrinth. Warm water stimulation would produce the opposite effect by increasing the vestibular tonic impulses from the side of stimulation. The test is done by administering to the tympanic mambrane of each side separately, an equal amount of cool or warm water in equal time periods, and determining the time from the onset of the stimulation to the end of the produced nystagmus. Further refinement of this test may be accomplished by the use of differential calorics (use of a measured amount of both cool and warm water in each ear),

and by the use of electronystagmography to quantitatively evaluate the response.

Because of the proximity of the auditory apparatus and nerve to the labyrinth and vestibular nerve, examination of hearing assumes major importance to verify and supplement impressions formed from the history and vestibular examination. A full discussion of the auditory examination goes beyond the scope of this paper. Gross clinical hearing and speech discrimination tests should be augmented by referral to the audiologist or ear, nose and throat specialist when any question of dysfunction exists. By audiograms and other evaluations they may be able to localize hearing disturbance to a relatively specific anatomic location.

CAUSES OF TRUE VERTIGO

The reasons for true vertigo, as mentioned earlier, can be classified into two general categories on an anatomic basis, i.e. central or peripheral. Nystagmus of peripheral origin is usually episodic and proportional to the symptoms of vertigo, while nystagmus of central causes is much more persistent and the accompanying vertigo may be transient, mild or absent. Central nystagmus is usually gaze-evoked and bidirectional with the quick component (direction) being in the direction of gaze. Vertical or dysconjugate nystagmus usually indicates a central mechanism. Tinnitus and hearing loss, if present, usually indicates a peripheral lesion. Other central nervous system involvement would tend to support central causes while cranial nerve involvement adjacent to the eighth cranial nerve would suggest a lesion in the cerebellopontine angle. Some of the differentiating features are given in TABLE I.

TABLE I

DIFFERENTIATING FEATURES OF PERIPHERAL AND CENTRAL NYSTAGMUS

FEATURE	PERIPHERAL	CENTRAL
Duration	Less than three weeks	Permanent
Direction	One only	Multidirectional
Character	Conjugate	Dissociated (often)
Effect of removing fixation	Enhanced	Unchanged, inhibited

Confusing possibilities are generated by those conditions that may cause both peripheral and central nystagmus. An acoustic neuroma may initially affect the eighth nerve and later also directly impinge on the brain stem. Basilar-vertebral insufficiency may cause either or both central and peripheral nystagmus. Disturbance of a vestibular end-organ usually causes decreased or absent function of that end-organ and only rarely by irritation causes hyperfunction or overactivity. The clinical result illustrates, acutely, the unbalanced effect of the normal but unopposed labyrinth, with resulting nystagmus toward the uninvolved side.

Some of the causes of peripheral vertigo can be broken into three main groups — vertebral-basilar insufficiency, Meniere's disease, and vestibular neuronitis. Some of the causes which occur less frequently may produce more severe vertigo.

Vertebral-basilar insufficiency can cause either central or peripheral vertigo (and nystagmus) by causing temporary ischemia to the brain stem or labyrinth, respectively. Peripheral vertigo of this etiology would generally last only a few seconds to minutes, be induced by sudden changes in head position or posture and seldom have accompanying signs of brain stem involvement, although

nausea may be present. It is more frequent in men over forty-five years of age. Caloric testing and testing for positional nystagmus are normal unless permanent ischemic damage has been done.

Meniere's disease is characterized by recurrent, sudden attacks of severe vertigo, frequently accompanied by nausea and vomiting. Tinnitus and hearing loss, if present, are aggravated during an attack or come with the vertigo. The cause is thought to be a recurrent distention of the endolymphatic system of one labyrinth for unknown reasons. Permanent damage eventually results. Testing will reveal unilateral sensioneural deafness of lower frequencies and abnormal vestibular function of the affected side.

Vestibular neuronitis, frequently diagnosed as acute labyrinthitis, is of unknown etiology, but is thought to be viral-infectious or toxic in origin, affecting the vestibular ganglion or nerve. This condition presents with the sudden and often complete loss of vestibular function of one side without associated hearing loss. It usually affects young to middle-aged adults and is characterized by the sudden onset of intermittent or persistent severe vertigo often accompanied by nausea and vomiting. The vertigo may be provoked or intensified by motion of the head. The frequency and intensity of the vertigo usually subsides gradually over a two- to three-week period but may persist intermittently for several years. Caloric testing during the acute phase shows decreased or absent function of the involved labyrinth which may be permanent.

Benign paroxysmal vertigo is a symptom complex often found as a residual of any significant vestibular end-organ disease. The pathophysiology of this set of symptoms is not understood but it does have certain identifiable features. Vertigo is produced

by sudden position changes of the head, occurs after a short latent period, lasts only a brief time and cannot be reproduced without a recovery period. This condition is the symptom analog of the earlier discussed benign positional nystagmus.

Other causes of vertigo are peri-labyrinthitis, the involvement of the perilabyrinthine endosteum by an eroding cholesteatoma; purulent labyrinthitis, which is due to direct spread of infection to the labyrinth from the middle ear; acoustic neuroma, a tumor of the eighth cranial nerve usually within the internal auditory meatus which presents early with a sensioneural hearing loss and less often with vertigo; and the ototoxic drugs, such as streptomycin, kanamycin, polymyxin B, ristocetin, and vancomycin which may damage vestibular or cochlear function (or both) irreversibly.

In central vertigo the brain stem is often involved. The type of disease process affecting the brain stem is less important to the production of symptoms than is the localization of damage. Among the most common of these are arteriosclerosis, other vascular diseases, and mass lesions of the brain stem. In the case of arteriosclerosis, vertebral-basilar insufficiency or occlusion may cause transient or permanent ischemia of the brain stem connections of the vestibular system, causing not only vertigo and nystagmus, but often diplopia, dysarthria, ataxia, visual defects, weakness and sensory loss. Other vascular diseases of the central nervous system such as meningovascular syphilis or Cogan's syndrome (thought to represent a collagen disease affecting the ocular, auditory and vestibular systems causing blurred vision, blindness, tinnitus, and deafness) may cause vertigo. Tumors of the brain stem causing disruption of pathways similar to those mentioned above may cause not only vertigo and nystagmus, but other manifestations of cerebellar and brain stem dysfunction as well.

Epilepsy and migraine attacks may be preceded in some patients by a vertiginous aura. In some migraine attacks the vertigo accompanies the headache and in others it may be the principle manifestation. Certain drugs such as toxic amounts of dilantin or barbiturates, may affect the central nervous system causing vertigo. Alcohol and even tobacco smoke in some susceptible individuals may cause nystagmus. Nystagmus, and less often vertigo, is a common manifestation of multiple sclerosis. Cerebellar lesions rarely cause vertigo by themselves, but a process involving the cerebellum and brain stem together may have vertigo as a manifestation. Supratentorial lesions rarely are responsible for vertigo, but if vertigo is due to such a lesion, it has little localizing value but may be suggestive of lesions in the temporal lobe area.

CAUSES OF NON-VERTIGINOUS DIZZINESS

Terms such as lightheadedness, faintness, or confusion are often used to describe "dizziness" which is nonvertiginous. This "dizziness" is usually related to circulatory, psychic or post-traumatic central nervous system disturbances. Psychologically determined symptoms are often confusing; they may be described in terms that suggest vertigo or may follow a true experience of vertigo. In the first instance, malingering or hysteria may underlie the complaint and be difficult to assess. Following an episode of vertigo or recurrent vertigo patients may manifest an unreasonable fear (phobia) of recurrence which is in itself disabling.

The circulatory causes for dizziness are those which cause relatively acute cerebral anoxemia. Some common inciting conditions are postural hypotension, cardiac arrhythmias, vasomotor collapse, myocardial infarction, and

a hypersensitive carotid sinus. This form of dizziness is most closely related to, but a lesser form of, syncope. It is characterized by its rather short duration and association with cardiovascular and respiratory abnormalities. Another form of dizziness, without vertigo, is that seen following trauma to the head, in what is commonly referred to as the post-concussive syndrome. This may also include chronic symptoms of headache, fatigue, and lack of concentration each of which generally shows improvement with time. It is important to recognize that true vestibular disturbances may also result from either cardiovascular disease or trauma affecting the vestibular end-organ.

COMMENT

One may state without fear of contradiction that determining the pathophysiology and etiology of dizziness is often difficult and sometimes impossible. The task is made less arduous if the physician has a firm grasp of the physiology involved and is aware of the various syndromes as outlined above. Often the major value to the patient evolves from the capacity of the knowledgeable physician to properly pursue those cases where a significant remediable lesion may be found but to treat symptomatically, without excessive evaluation, that majority of individuals who will recover spontaneously.

References

Bernstein L: Peripheral causes of vertigo. Consultant January 1967

Cogan DG: Neurology of the Ocular Muscles. Springfield: Charles C. Thomas, 1956

Dix MR: Modern tests of vestibular function with special reference to their value in clinical practice. Brit Med J 3:317-323, 1969

Fields WS, Alford BR (eds): Neurologic Aspects of Auditory and Vestibular Disorders. Springfield: Charles C. Thomas, 1964

Grinker RR, Sahs AL: Neurology. Springfield: Charles C. Thomas, 1966

Hay RH: Vertigo. Its commoner neurologic causes. Consultant January 1966

Hyland HH: Vertigo and dizziness. IN Signs and Symptoms. MacBryde CR (ed). Philadelphia: J. B. Lippincott Co., 1964

Peele TL: The vestibular system. IN The Neuroanatomic Basis for Clinical Neurology. New York: McGraw-Hill Book Co., 1961

Wolfson RJ, Myers D, Schlosser WD, et al: Vertigo. Ciba Clinical Symposium. Walton JH (ed). 1965

Peripatetic, *adj.* Walking about. Relating to the Philosophy of Aristotle, who, while expounding it, moved from place to place in order to avoid his pupil's objections. A needless precaution—they knew no more of the matter than he.

Phrenology, *n.* The science of picking the pocket through the scalp. It consists in locating and exploiting the organ that one is a dupe with.

Preference, *n.* A sentiment, or frame of mind, induced by the erroneous belief that one thing is better than another.

An ancient philosopher, expounding his conviction that life is no better than death, was asked by a disciple why, then, he did not die. "Because," he replied, "death is no better than life."

It is longer.

AMBROSE BIERCE. *circa 1880*
The Devil's Dictionary
(New York: Dover, 1958)

POST SURGICAL PSYCHOSIS

MAJ Lynn B. Gerow, Jr., MC

There are a variety of psychological reactions in patients before and following surgery. Feelings of helplessness or of being punished are common and patients often find it difficult to tolerate frustration or delay of gratification. They may make great demands on the staff or may substitute thought for action which, for example, may take the form of minor restlessness or a major decision to cancel surgery and leave the hospital. A patient's thoughts are likely to be dominated by fantasy material about his doctor, the nurses, or the circumstances surrounding his condition. The patient may become excessively dependent and express a strong desire to be cared for.

A person's ability to recover from these symptoms varies widely depending upon whether or not his illness has been successfully ameliorated by surgery, the duration and severity of his psychological symptoms, and his ability to adapt to the adversities and vicissitudes of normal living.

The patient may experience some, none, or all of these psychological reactions. Certainly each case is different and must be considered individually. This paper will describe the post-operative psychotic episode and an approach to the management of this condition.

Recognition of psychosis on a surgical service is not always easy. Moreover, the psychological problems dealt with in orthopedics, ophthalmology, gynecology, plastic surgery, urology, and general surgery will vary. I will

confine this discussion to psychosis occurring in the patient after heart surgery. This usually takes the form of an acute brain syndrome followed by a psychotic depressive reaction. Postoperative psychosis occurs in one of every 1500 general surgery patients; however, it has been reported in early studies in a range of one to 19 percent in the postcardiac surgery population.

Kornfield et al /1/ studied patients with open heart surgery to elucidate the type of psychiatric disturbance, its incidence, and contributing factors to the psychiatric disturbance, especially problems of the intensive care unit. One hundred nineteen patients were studied who had had open or closed heart surgery. Each had survived at least one month. Twenty patients were interviewed by a psychiatrist. The incidence of postoperative psychosis in this subgroup was 70 percent. In the total group the incidence was 38 percent. Another investigator who interviewed all patients in his study group found an incidence of 57 percent.

The usual clinical picture was the onset of delirium two to four days postoperatively. /1/ Usually the patient would experience illusory phenomenon (e.g. sounds emanating from somewhere in the room), and a rocking or floating sensation which would be followed sometime later by auditory and visual hallucinations and paranoid ideation. The patient would become disoriented to time, place and person.

In the Mayo study /2/ age, sex, marital status, rheumatic heart disease, and length of congestive heart failure were not found to be significant variables related to incidence of psychosis. However, the ajudged severity of risk for anesthesia was a significant correlate. Duration of the procedure, bypass time, and hypothemia taken individually were not significant; however, these taken together were significant especially with double valve procedures. There was no incidence of delirium in children and

in closed heart mitral commissurotomy.

The question is always raised as to whether or not these phenomena of perceptual distortions, hallucinations, disorientation, and paranoid ideation have an organic or functional etiology. The reader is referred to Gilman /3/ for an excellent study of neurologic disturbance following open heart surgery. In this study the etiology was the result of insufficient cerebral blood flow or embolic disease. The symptomatology was different and was manifested by gnostic disorder, hemiplegia, visual field defect, or convulsive disorder. Psychotic symptoms were not observed in these patients.

To return to the patients who did experience a psychotic episode following surgery, it is noteworthy that a lucid period followed surgery for 2-4 days before the onset of the psychotic disturbance. Also the onset of this form of psychosis closely resembles the psychosis secondary to sleep and sensory deprivation and the symptoms disappear with sleep or transfer from the intensive care unit. Many studies have described psychosis secondary to sleep deprivation as resembling delirium at night and paranoid schizophrenia in the daytime. More appropriately it seems likely that delirium represents a final common pathway developing after impaired brain functioning, chronic cardiac disease, a long operation and bypass, and reduction in sleep and sensory stimuli. /4/

Treatment of these patients early and vigorously can be life-saving. /5/ Early recognition and thorough re-examination of the general medical status is imperative. Careful review of medications which are known to produce psychosis, depression, or anoxia should be emphasized.

Phenothiazines may be warranted. Mellaril(R) (thioridazine hydrochloride) is often useful up to 100 mg four times daily; however, much

smaller doses are the rule. A private room with continual observation should be considered. Restraints may be needed. The patient should be repeatedly reassured and oriented. A light is helpful at the bedside. Strangers, as well as nonessential medical tests, should be kept to a minimum. A clock, a calendar, and the patient's own clothes at the bedside will help overcome his disorientation. No conferences should be held outside the patient's door because they tend to confuse the patient and lead to distortions and increasing paranoid ideas. Glasses and hearing aids should be returned to the patient as soon as possible. Although there is a medical team approach in these complicated cases, one doctor should be designated as primary physician and spokesman to the patient for the group.

This short review suffers from incompleteness, but I hope it serves as an overview of an important, life-threatening, but treatable, psychiatric disorder which occurs commonly in the immediate postoperative period.

References

1. Kornfeld DS, Zimberg S, Malm JR: Psychiatric complications of open-heart surgery. New Eng J Med 273:287-292, 1965
2. Burgess GN, Kirklin JW, Steinhiber RM: Some psychiatric aspects of intracardiac surgery. Mayo Clin Proc 42:1-12, 1967
3. Gilman S: Cerebral disorders after open-heart operations. New Eng J Med 272:489-498, 1965
4. Morse RM, Litin EM: Postoperative delirium. A study of etiologic factors. Amer J Psychiat 126:136-142, 1969
5. Hall RCW, Reading A: Psychosocial factors in medicine. Steroid psychosis. New Physician 20:20-23 (Jan) 1971

NEUROMUSCULAR JUNCTION AND ITS DISORDERS

MAJ Garland E. McCarty, MC*

PHYSIOLOGY AND PHARMACOLOGY OF THE NEUROMUSCULAR JUNCTION

Acetylcholine (ACh) is synthesized by a two-step acetylation procedure from choline. In the first stage acetylcoenzyme A is formed from acetate in the presence of the "acetate-activating" enzyme acetylkinase. The second stage involves the transfer of the acetyl group from acetylcoenzyme A to choline, in which the specific catalyst is choline acetylase to form acetylcholine. The major energy source of these reactions is provided in the form of energy rich bonds of adenosine triphosphate synthesized in carbohydrate metabolism.

Acetylcholine has two particular actions in the body, these being a muscarinic effect and a nicotinic effect. The alkaloid muscarine exerts effects similar to those of ACh on smooth muscles, cardiac muscle and exocrine glands without having an effect on ganglionic transmission or skeletal muscle. Nicotine has a predilection for blocking ganglia following initial stimulation. It also acts on neuromuscular transmission. Therefore, the effects of ACh on smooth muscle, cardiac muscle and exocrine glands is termed muscarinic effect and the effects of ACh on ganglia and skeletal muscle is called nicotinic effect. The muscarine receptors are the atropine sensitive receptors. The nicotinic receptors may be

*Formerly Resident, Neurology Service, Letterman General Hospital and presently staff neurologist, Brooke General Hospital, Fort Sam Houston, Texas

divided into the ganglionic receptors which are hexamethonium sensitive and the skeletal muscle receptors which are sensitive to d-tubocurarine.

Acetylcholine is hydrolyzed by the cholinesterases to form acetic acid and choline. Acetylcholinesterase, also known as true cholinesterase or cholinesterase I, is found in the nervous system, red cells and human placenta. Its greatest activity is against acetyl esters. Nonspecific cholinesterase, also known as pseudocholinesterase or cholinesterase II, has its greatest activity against butyrl esters. The destruction of acetylcholine is so rapid that the refractory period of the neuron allows sufficient time for the inactivation of the transmitter released from the prejunctional fibers. Other means of removing ACh, such as its diffusion from muscle or ganglia into the extracellular fluid and hence into the blood stream or its restitution to presynaptic terminals in a manner analagous to the uptake of choline, probably have little importance.

In the region of the neuromuscular junction the muscle fiber displays an accumulation of sarcoplasm which produces an asymmetric swelling, the Doyère eminence. Figure 1. The sarcoplasm in this region is rich in sarcomeres (muscle mitochondria) and contains several nuclei, the "sole-plate nuclei". As the motor axon approaches, it loses its myelin sheath and forms a branch of complexly convoluted endings partly embedded in trough-like depressions in the muscle plasma membrane.

In the region of the synaptic gutters, the protoplasmic membrane of the muscle fiber, termed the "sarcoplasmic membrane", is thrown into complex folds. The portions of the axon terminal which are not surrounded by the

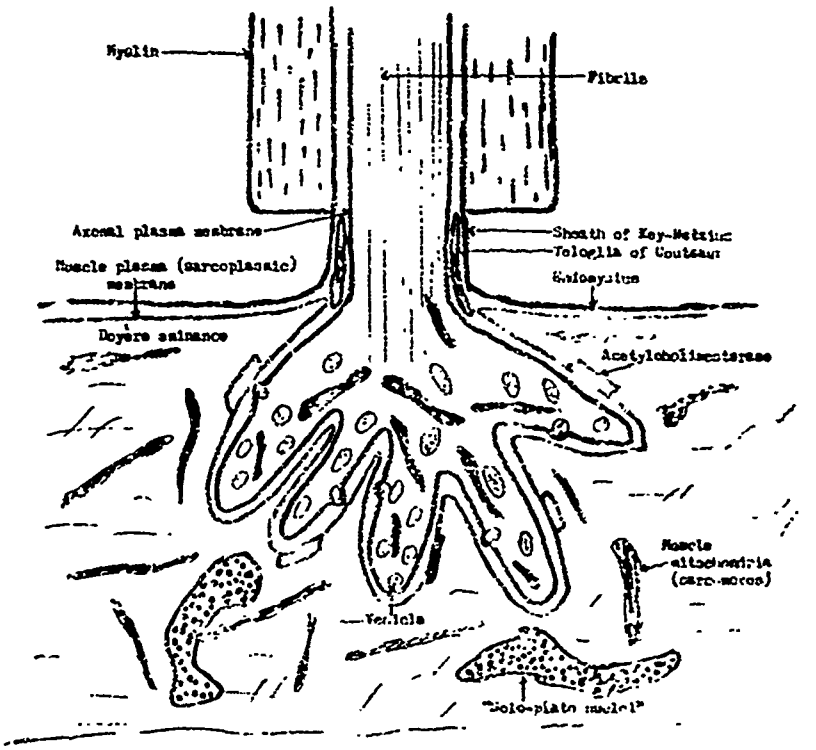


Fig. 1. Schematic drawing of neuromuscular junction.

synaptic gutters, are covered by a thin, cellular sheath, the "teloglia" of Couteaux (nuclei of which are probably identical with the arborization nuclei of Kuhne). Thin cytoplasmic extensions of these cells cover all portions of the axon terminal which are not embedded in the synaptic gutter and follow the branches of the axon terminal closely. They do not extend into the adjacent

muscle plasma membrane, nor are they interposed between it and the axonal plasma membrane, except for very short distances at the outer borders of the synaptic gutter. The connective tissue sheath of the axon (sheath of Key-Retzius) does become continuous with the fine connective tissue envelope of the muscle fiber, the endomysium. The plasma membranes of the two structures remain distinct and separate.

The axon terminal contains many mitochondria which vary in shape from ovoid to cylindroid. In addition, the terminal axoplasm contains many circular to irregular ovoid profiles, 300-580 Å in diameter which are vesicular in nature and are disposed in greatest concentration near the synaptic membrane and are more sparce in the central regions of the terminal axoplasm. The function of these synaptic vesicles is to synthesize, store and transfer the ACh. The view that the transmitter synthesis arises in mitochondria has now been rejected largely on evidence from centrifugation studies which have confirmed the close association of choline acetylase, the enzyme involved in the synthesis of ACh, and the small granule microsomes. ACh is stored in a protein-bound form probably associated with choline acetylase but protected from cholinesterases both within synaptic vesicles ("bound") and without ("surplus" or "free"). Bound acetylcholine, which is physiologically inactive, provides the store from which the transmitter is released. By electronmicroscopy the synaptic vesicles have been seen to lie in close apposition to the axonal plasma membrane, which, in turn, has frequent circular depressions with a diameter similar to that of the synaptic vesicles, suggesting the interpretation that the contents of the vesicles may be in the process of being secreted into the synaptic space. Also in the terminal axoplasm is a fine, fibrillar component, probably continuous with the

axonal neurofibrillae, which is present in the center portions of the axoplasm. It appears to bear a quantitatively inverse relationship to synaptic vesicles, i.e., where fibrils are numerous, vesicles are sparce and vice versa. Also in the terminal axoplasm are irregular aggregates of larger vesicular cysterns and tubules, mitochondria and ovoid contours 0.5-1.0 μ in diameter surrounded by a double membrane which contains closely packed circular profiles indistinguishable from those of synaptic vesicles.

The region of apposition between the axon terminal and the telolemmal cytoplasm is characterized by a double membrane, made up of the plasma membranes of the two cells, with a spacing of 200-250 Å. These membranes have an intricately folded and interdigitating appearance.

In the synaptic gutters the muscle plasma membrane is thrown into convoluted folds 0.2-0.4 μ apart and are approximately 1.0 μ thick. The sarcoplasmic membrane between the folds is closely applied to the axoplasmic membrane of the axon terminal, the distance between the two membranes is 500-700 Å. This intracellular space is termed the synaptic space.

The sarcoplasm underlying the neuromuscular junction contains elements of the sarcoplasmic reticulum, sarcomeres (muscle mitochondria), aggregates of dense granules 100-150 Å in diameter and "sole-plate" nuclei.

Cholinesterase seems to be located in the sarcoplasmic membrane and is oriented within this membrane in such a manner that the active groups face the synaptic side of the membrane. A small amount has also been found within the nerve fiber in the endoplasmic reticulum.

Release of Acetylcholine

Acetylcholine is liberated from the motor nerve endings in small, but multimolecular packets, or quanta. These quanta are liberated at low frequency and at random in the absence of a nerve impulse. The quanta may be detected by the small (0.4 mV) end-plate depolarizations which they produce (spontaneous miniature end-plate potentials). It has also been demonstrated that the end-plate potential in response to a nerve stimulus is the result of the simultaneous release of hundreds of these quanta of ACh.

While the size of the miniature end-plate potentials may be varied by altering the end-plate responsiveness to ACh (e.g. with d-tubocurarine or anticholinesterase), there has been no evidence that the size of the quantum varies under a wide variety of experimental conditions. The number of quanta does vary however and is increased by depolarization of the nerve terminals, by calcium ions, during post-tetanic facilitation and by stretching the nerve terminals. The number of reduced by magnesium ions, botulinum toxin and hyperpolarization of the nerve terminals. Therefore, it can be seen that the resting motor nerve terminal liberates minute, but multimolecular packets of ACh (quanta) at low frequency and at random. However, the arrival of a nerve impulse depolarizes the nerve terminal and releases hundreds of these quanta of ACh simultaneously.

The neuromuscular junction functions as an "amplifier" to increase the minute currents generated by terminal fibers into currents with sufficient strength to excite the muscle fibers. Electrical studies show that the current generated by the nerve fiber itself

is far less than the threshold value required to stimulate the muscle fiber. However, by causing the release of ACh, an end-plate potential is generated that is much stronger than the nerve potential itself and can therefore excite the muscle fiber.

The application of ACh to the receptor sites of the end-plate produces a depolarization which is greater than that explicable on the basis of inward conduction of ACh ions alone. This depolarization is caused by an increased permeability, or conductance, to sodium, potassium and perhaps other ions triggered by ACh. The end-plate depolarization produced by ACh liberated by a nerve volley produces the end-plate potential.

Under normal circumstances three safety factors exist to insure depolarization: (1) ACh is liberated in excess, (2) depolarization is not dependent upon the ACh ion flux, but is the result of the much larger ion fluxes provided by the ACh-induced permeability increase, and (3) this chemically induced depolarization of the end-plate (from -90mV to -15mV) excedes the depolarization necessary to initiate the propagation of a muscle action potential (from -90mV to -50 mV).

Neuromuscular Block

Types of neuromuscular transmission block may be characterized by the abnormality of end-plate depolarization. One type is caused by insufficient depolarization of the end-plate due to diminished synthesis or release of ACh, or secondary to the presence of a substance which competes with ACh for the receptor sites but which does not produce depolarization (competitive blocking agent). The second type of block is the result of persistent depolarization of the end-plate

produced by a stable depolarizing agent, or by persistence of ACh itself caused by inhibition of cholinesterase. A third type of block has been postulated. This hypothesis states that the application of a depolarizing substance (including ACh) to the end-plate not only produces depolarization, but also reduces the end-plate's sensitivity to depolarization. Restoration of desensitized receptors to the sensitive state occurs rapidly upon withdrawal of the depolarizing substance. This restoration of sensitivity, however, is retarded by persistence of the depolarizing substance. The desensitization block shares some of the properties of the block produced by competitive substances in that transmitter is unable to produce its usual amount of depolarization. When transmitter concentration is enhanced (e.g. by an anticholinesterase) the competitive block may be reversed; reversal of the desensitization block is limited under these circumstances by the amount of receptor in the desensitized state. Furthermore, persistence of transmitter would retard restoration of sensitivity. Figure 2.

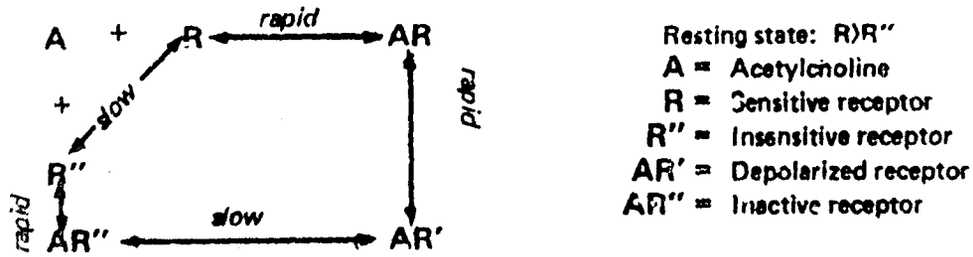


Fig. 2. Under resting conditions receptor is distributed between its sensitive (R) and insensitive (R'') forms with R)R''. ACh (A) combines rapidly with R to form a complex (AR) and alters the receptor so that it is depolarized (AR'). A also combines rapidly with the small amount of R'' to form an inactive complex (AR''). With prompt removal of A (by esterase or diffusion) the reverse reactions occur promptly. However, with persistence of A the slower desensitizing reaction occurs converting depolarized receptor complex (AR') into its inactive form (AR''), thus reducing depolarization. With removal of A the reverse reaction occurs rapidly, but since receptor is left in the inactive state (R'') a subsequent application of A will then find less R for conversion to AR' (depolarization). Sensitivity is restored in the absence of A by the slow reaction R''←→R. This hypothesis is important since an abnormal distribution of desensitized receptor (R'')R) would explain many features of the myasthenic block in neuromuscular transmission.

Other Forms of Neuromuscular Transmission

Two additional forms of neuromuscular transmission have been demonstrated, other than the transmission of excitation from nerve to muscle. Studies have shown that the surgical crossing of the motor nerves from "fast" (white) muscles and "slow" (red) muscles makes the "fast" muscles slow, and the "slow" muscles fast. Thus, it would appear that motor neurons in some manner transmit to muscle their characteristic property of contracting rapidly or slowly. It has also been shown that denervated muscle fibers promptly acquire sensitivity to externally applied ACh over their entire surface. Viewed conversely, intact motor nerves exert an influence with restricts the muscle fiber's ACh sensitivity to the motor end-plate.

CLINICAL CONDITIONS

Myasthenia Gravis

Myasthenia gravis is a disease characterized by a variable weakness following the use of voluntary muscles, particularly those subserving ocular movements, facial expression, mastication, deglution and respiration. This affliction was first described by Thomas Willis in 1672 and designated "bulbar palsy without visible anatomical changes". Cardiac and smooth muscles are usually not affected although some reports state that myocardial changes are present in fifty percent of the cases. Muscles of the neck, trunk and limbs are usually involved and respiratory difficulty occurs in severe cases. At first the weakness takes the form of a failure to contraction after

any maintained effort, but in more severe phases of the disorder, the muscles first and most severely affected cease to contract even after prolonged rest. Since the disorder appears to have no relationship to the phenomenon of fatigue, except that both require a certain amount of contraction, the use of the word fatigue in relation to myasthenia is incorrect. A complete definition of the disease should include the ability of anticholinesterase drugs to reverse the greater part of the weakness induced by use of the muscles and the ability of the weak muscles to respond to direct stimulation.

The prevalence is three per 100,000 and it is slightly more common in the female than the male. (Before the age of forty years females are much more frequently affected. After this age there is a slight preponderance in the male.) The peak incidence for females is 15-35 years of age and that for males is 30-45 years of age. It may occur at any age although it is rare for the first signs to appear before the age of ten or over the age of seventy. A familial incidence in siblings has been recorded several times but hereditary liability to the disease is rare. When it is present in one twin, the other one will usually be spared.

The onset is usually insidious without an obvious cause. In the early stage, the symptoms may be present only after exercise or at the end of the day, but in the severe stage of the disease, the muscular weakness is constant. Occasionally the onset is sudden, with extensive paralysis of the bulbar and spinal muscles. Weakness may be generalized or confined to a restricted group of muscles, particularly those supplied by the nuclei of the brain stem. Involvement of the ocular muscles is the most common presenting symptom, occurring in approximately forty percent of the cases. Muscles of the trunk and extremities

are involved first in about one-third of the cases and the palatal or pharyngeal muscles in twenty percent. Smooth muscles are occasionally involved becoming abnormally fatiguable. It has been observed that the sphincter of the iris may fatigue on prolonged contraction in response to light. Two cases have been reported in which there was a disturbance of taste sensation and three cases in which perioral and lingual paresthesias were present — all which improved on prostigmin. Pain may occur in myasthenia gravis and has been reported in as high as four percent as the presenting symptom. The mechanism most often is holding the head back in order to see in the presence of ptosis which results in an arching of the neck muscles or low back.

The physical examination is usually normal except for weakness of the involved muscles. The frequency of weakness of the facial and levator palpebrae muscles produces a characteristic expressionless facies with drooping of the eyelids (myasthenic facies). When the ocular muscles are involved there may be ptosis, diplopia and nystagmus. The sensory examination is normal and the reflexes are preserved even in muscles which are totally unable to perform any voluntary movement. Muscle atrophy of varying degrees is reported in approximately ten percent of cases. Crisis, either myasthenic or cholinergic, occurs in thirty to forty percent of the cases. The incidence for the crisis is higher in the first two years after onset. TABLE I gives the signs and symptoms of crisis.

TABLE I

SIGNS AND SYMPTOMS OF MYASTHENIC AND CHOLINERGIC CRISIS

Myasthenic

- Ocular ptosis
- Dysarthria or anarthria
- Dysphagia or aphagia
- Dyspnea or apnea
- Facial weakness
- Masticatory weakness
- Difficulty handling secretions
- General weakness

Cholinergic

Muscarinic Signs and Symptoms	Nicotinic Signs and Symptoms
Sweating	Muscle fasciculations
Lacrimation	"Thick tongue"
Salivation	Dysarthric speech
Anorexia	Dysphagia
Abdominal cramping	Trismus
Diarrhea	Muscle cramps and spasms
Nausea and vomiting	General weakness
Urinary frequency	Signs and Symptoms
Incontinence of bowel and bladder	Restlessness
Miosis	Anxiety
Blurred vision	Giddiness
Bronchorrhea	Vertigo
Dyspnea and wheezing	Headache
Substernal pressure	Confusion and stupor
Bronchospasm	Coma
Pulmonary edema	Convulsions

The clinical course may be one of remissions and exacerbations. The prognosis for relief of symptoms by treatment is best in the patients with involvement of the trunk and extremity muscles. Ocular paralyses are more refractory to therapy and require relatively large doses, however these represent the most benign form of the disease. The ultimate prognosis is poorest in patients with dysphagia, dysarthria and weakness of the respiratory muscles. Sudden unexpected deaths have resulted and may be the result of cardiac or respiratory failure. Seventy to eighty percent of deaths occur within ten years of onset of disease.

Differential diagnosis includes the muscular dystrophies, amyotrophic lateral sclerosis, progressive bulbar palsy, ophthalmoplegias of other causes, perivenous encephalomyelitis, hyperthyroidism, asthenia of psychoneurosis, Lambert-Eaton syndrome, multiple sclerosis and polymyositis. Cases of neuromuscular defect similar to myasthenia gravis with similar findings on the EMG have been reported in amyotrophic lateral sclerosis. One should be aware that slight benefits from anticholinesterase drugs are occasionally observed in nonmyasthenic patients. The favorable response in such cases is chiefly subjective, objective improvement being minimal or absent.

Etiology

It is now well established that myasthenic end-plates differ from those of normal individuals in several respects: (1) its sensitivity to intra-arterially injected ACh is decreased; (2) the intra-arterial injection of choline, rather than the depolarizing block produced in normal individuals, cause a nondepolarizing block in myasthenic patients; (3) myasthenic end-plates are less sensitive to decamethonium and succinylcholine requiring three to four times the normal dose of decamethonium to lessen a test contraction to electrical stimulation of the nerve; (4) the decamethonium-induced neuromuscular block is reversible by neostigmine or edrophonium whereas in normal subjects a decamethonium block of moderate degree is non-ACh-inhibitory and non-ACh-reversible (depolarizing), while a decamethonium block of marked degree is ACh-inhibitory and ACh-reversible (competitive); and (5) the myasthenic end-plate while exhibiting a decreased sensitivity to depolarizing neuromuscular blocking agents is excessively sensitive to d-tubocurarine.

The theories for the cause of myasthenia are numerous and include (1) a defect in the synthesis or liberation of ACh at the motor end-plate; (2) an unusually rapid breakdown of ACh from the overactivity of cholinesterase; (3) the resistance of the end-plate to the depolarizing effects of ACh might be caused by the continuous or prolonged exposure of the neuromuscular junction to a depolarizing agent; (4) the resistance to depolarization by ACh may be due to ultramicroscopic changes in the chemical structure of the receptor substance; (5) the defect in neuromuscular transmission may be due to an acetylcholine (ACh-inhibitory) block produced by ACh released in a normal manner during neuromuscular transmission, or by choline formed following hydrolysis of endogenous ACh. This block produced by ACh is ACh-reversible in some patients and non-ACh-reversible (ACh insensitive) in others. Since an ACh-reversible block can be rendered ACh-insensitive by the repeated administration of ACh or by prolonged nerve stimulation, it is suggested that in myasthenic patients there may be one or more abnormal forms of receptor substance or of combinations of ACh with receptor substance, and that the predominant form may determine the nature of the block, the clinical state of the patient, and his response to anticholinesterase medication.

In the EMG the most characteristic abnormality is the irregularity and eventual loss of the voltage in the spikes of single units, presumed to be due to variation in the number of fibers contracting to each nerve impulse. When the nerve to the muscle is stimulated electrically by a rhythmic series of shocks, the response fails progressively (myasthenic reaction). If a high frequency of stimulus is used (200-500 stimuli/sec), an additional phenomenon is observed; a strong twitch to the first shock, followed by only a poor contraction. This is the Wedensky phenomenon, which means that the first impulse of the rapid

series was the only one to excite many of the fibers. It is observed only at much higher frequency of stimulus in normal muscle, and was shown by Wedensky to be due to the fact that the rate of stimulus is so fast that each subsequent stimulus falls into the relative refractory period of the one before, and therefore excites only a subnormal nerve impulse. The subnormal impulses, although insufficient to excite the muscle fiber, each set up yet another refractory period. The phenomenon therefore is one way of measuring the refractory period of the conducting system (nerve and neuromyal junction) and its occurrence at low frequencies in myasthenia gravis patients and in curare poisoning indicates that at some point near the nerve terminals (not necessarily the end-plate) the refractory phase of the excitatory process is prolonged. All these abnormalities are reversed by anticholinesterases.

In eighteen to sixty-eight percent of patients with myasthenia gravis, serum globulin, particularly the IgG fraction, reacts with skeletal muscle, cardiac muscle, and thymic epithelial cells as well as nuclei of various other tissues. These findings indicate a possible role of the serum globulin in the pathogenesis of myasthenia gravis. However, there is no evidence that the serum globulin is directly responsible for the neuromuscular block in myasthenia gravis patients; in fact, after administration of serum from patients with high titers of muscle antibody to other myasthenia gravis patients, neuromuscular transmission improves, suggesting that the globulin may exert a protective effect.

Approximately fifteen percent of infants born to mothers with myasthenia gravis develop respiratory and feeding difficulties and often more generalized weakness which responds to cholinergic drugs. This condition of neonatal myasthenia was first

reported in 1942. Symptoms appear within seventy-two hours after birth and persist for several days to three months. The implication is that a factor influencing neuromuscular transmission crosses the placenta, and that this factor, or its effect persists for many weeks without leaving a permanent defect.

Diagnosis

The diagnosis of myasthenia gravis is made from the history, physical examination, repetitive nerve stimulation and recording strength of muscular contraction on EMG, Tensilon®test and Tensilon®tonography.

Pathology

In occasional cases focal collections of small lymphocytes or "lymphorrhages" first described in 1905 by Buzzard have been found surrounding small venules or capillaries in the interstitial tissue of affected muscles. However these lymphorrhages are often not found in typical cases of myasthenia. In addition to these lymphorrhages, foci or more obvious muscle damage have been described including atrophy and coagulative necrosis of isolated muscle fibers in close proximity to the cellular infiltrates. These have also been found in the upper digestive tract, heart, and diaphragm.

Relationship to Thymus

In 1901 a case of thymic tumor in a patient with myasthenia gravis was reported and since that time a definite relationship between the thymus gland and myasthenia gravis has been established. The abnormality of the thymus in myasthenia patients without thymoma consists of varying degrees of lymphoid hyperplasia which is notable for the presence of germinal centers in the medulla. In

thymoma associated with myasthenia gravis, epithelial cells and lymphocytes are prominent; in thymoma not associated with myasthenia, spindle-shaped cells predominate. The incidence of thymoma in patients with myasthenia gravis is approximately fifteen percent (an increase of 5,000 times over that in patients without myasthenia) and the incidence of myasthenia in patients with thymoma is about seventy percent. Approximately twenty-five percent of thymomas are malignant. From the clinical standpoint, the presenting symptoms of myasthenia gravis in thymoma patients is indistinguishable from that seen in non-thymoma patients. Often, however, the case is more fulminating, more difficult to manage, usually appears in the middle or older age group and is unusual under the age of twenty years. In Perlo, Schwab and Castleman's study thymoma was discovered after the onset of myasthenia in fifty-one patients. In five patients the diagnosis of myasthenia gravis followed the diagnosis of thymoma. Also in their study, tumor is demonstrable by roentgenogram in the majority of cases.

It is generally agreed that patients with thymoma and myasthenia gravis do not gain the degree of relief of weakness from thymectomy seen in non-thymoma myasthenic patients. Despite this less satisfactory experience with the removal of thymomas in myasthenic patients, the operation is recommended in addition to treatment of the mediastinum with pre- or postoperative X-ray therapy. The prognosis is especially poor if the tumor is malignant. There has been reliably reported a complete remission in seventeen percent and considerable improvement in twenty-nine percent of the operated cases as compared to six percent remission and ten percent considerable improvement in the nonoperated cases. In the majority the improvement consists of an ability to perform their daily tasks on a smaller dose of anticholinesterase. In

Zeldowicz and Saxton's study of surgical versus non-surgical treatment for myasthenic patients who did not have a thymoma they showed that in a group of thirty non-thymoma patients treated medically, fifty percent of the patients derived moderate to good improvement (mean follow-up = eleven years). Ten percent of the patients in this group died from myasthenia. In the group of non-thymoma patients treated by thymectomy, eighty-three percent achieved good to excellent improvement. There was no surgical or myasthenic mortality over a mean follow-up of nine years. In their eight thymoma patients, there was no difference between surgical and medical management.

The lymphocyte count of the blood in normal individuals is fairly stable and varies between five to twenty percent. There has been no correlation between initial lymphocyte counts and severity of myasthenia however, serial absolute lymphocyte counts bear a relation to the clinical course in the majority of myasthenic patients. In general, a fall in lymphocyte count from the initial level is a favorable prognostic sign while a rising count reflects an unfavorable course. A high absolute lymphocyte count in a patient being considered for thymectomy is a favorable sign for benefit from operation. A low count means a less favorable prognosis from operation. A high absolute lymphocyte count preoperatively in thymectomy cases may presage immediate postoperative drug requirements.

Relationship Between the Thyroid and Myasthenia Gravis

The relationship between the thyroid and myasthenia gravis is frequently reported and hyperthyroidism is the usual thyroid state. However, hyperthyroidism has been found in three percent of myasthenic patients and evidence of myxedema in a further three percent. It has been proposed that in hyperthyroidism

there is excessive cholinesterase or an altered ACh/cholinesterase ratio.

Botulism

This condition is caused by an exotoxin liberated by Clostridium botulinum. As little as 0.05 mg of this toxin is fatal to man. It produces a total paralysis of cholinergic motor fibers and affects little or not at all the adrenergic motor fibers or the sensory fibers. Botulinus toxin exerts its paralytic action by a selective peripheral effect on the terminals of the axon inhibiting the release of ACh.

Black Widow Spider

Black widow spiders of the species Latrodectus produces a toxin which affects predominately the neuromuscular system and may prove fatal. It produces a heightened excitability of the neuromuscular apparatus.

Tick Paralysis

The wood tick, Dermacentor andersoni, and the dog tick, Dermacentor variabilis, elaborate a toxin causing a pronounced weakness of the muscles of the muscles of the arms, legs, respiration, and cranial musculature. The mechanism of action of this toxin is unknown but paralysis is usually produced only after prolonged feeding (five to seven days) on the host by a gravid female tick.

Tetanus

Caused by an exotoxin elaborated by the bacilli Clostridium tetani. As little as 0.22 mg of the toxin is fatal to man. The effect of the toxin is at the neuromuscular junction as well as on the motor synapses in the spinal cord and brain stem.

Recommended References

Adams RD, Denny-Brown D, Pearson C: Diseases of Muscle, 2nd edition. New York: Harper and Brothers, 1962

Burger A (ed): Drugs Affecting the Peripheral Nervous System. New York: Marcel Dekker, Inc., 1967

Brain, The Lord, Norris FH Jr (eds): The Remote Effects of Cancer on the Nervous System. Contemporary Neurology Symposia. Vol I. New York: Grune and Stratton, 1965

Glaser JS: Tensilon(R) tonography in the diagnosis of myasthenia gravis. Invest Ophthal 6:135-140, 1967

Kornfeld P, Somlyo A, Osserman KE: Role of calcium in myasthenia gravis. Arch Neurol 21:466-470, 1969

Kornguth SE, Hanson JC, Chun RWM: Antineuronal antibodies in patients having myasthenia gravis. Neurology 20:749-755, 1970

Namba T, Brunner NG, Brown SB,et al: Familial myasthenia gravis. Arch Neurol 25:49-60 (Jul) 1971

Namba T, Arimori S, Grob D: Lymphocytes of patients with myasthenia gravis. Arch Neurol 21.285-295, 1969

Papatestas AE, Alpert LI, Osserman KE, et al: Studies in myasthenia gravis. Effects of thymectomy. Amer J Med 50:465-474 (Apr) 1971

Perlo VP, Schwab RS, Castle B: Myasthenia gravis and thymoma. IN The Remote Effects of Cancer on the Nervous System. Contemporary Neurology Symposia. Vol I. Brain, The Lord, Norris FH (eds). New York: Grune and Stratton, 1964. pp 55-66

Viets HR (ed) Myasthenia Gravis Springfield: Charles C. Thomas, 1961

Warner WA, Sanders E: Neuromuscular blockade associated with gentamicin therapy. JAMA 215:1153-1154, 1971

Wise GA, McQuillen MP: Transient neonatal myasthenia. Arch Neurol 22:556-565, 1970

Wray S, Pavan-Langston D: A re-evaluation of edrophonium chloride (Tensilon(R)) tonography in the diagnosis of myasthenia gravis. Neurology 21:587-593, 1971

Zeldowicz LR, Saxton GD: Myasthenia gravis. A comparative evaluation of medical and surgical treatment. Canad Med Ass J 101:609-614, 1969

ACKNOWLEDGEMENT

Mrs. Frances Buchanan, wife of our Guest Editor, has prepared in final form the majority of the narratives of this symposium. Although not being paid, typing at home, communicating with the medical editor by telephone, she has made reality of this production possible. Writing for the editorial board and the readers, I wish to express our sincere appreciation to Mrs. Buchanan for a job well done and for myself especially, for the pleasure of working with her. L.A., Medical Editor

Radicalism, *n.* The conservatism of to-morrow injected into the affairs of today.

Rational, *adj.* Devoid of all delusions save those of observation, experience and reflection.

Reasonable, *adj.* Accessible to the infection of our own opinions. Hospitable to persuasion, dissuasion and evasion.

Recollect, *v.* To recall with additions something not previously known.

Reconsider, *v.* To seek a justification for a decision already made.

Reflection, *n.* An action of the mind whereby we obtain a clearer view of our relation to things of yesterday and are able to avoid the perils that we shall not again encounter.

AMBROSE BIERCE, *circa 1880*
The Devil's Dictionary
(New York: Dover, 1958)